NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGIES

Patisiran for treating hereditary transthyretin amyloidosis [ID1279]

Evaluation Committee Meeting – Tuesday 12 February 2019
2nd Committee meeting

The following documents are made available to the consultees and commentators:

1. **Evaluation Consultation Document (ECD)** as issued to consultees and commentators

2. **Consultee and commentator comment on the Evaluation Consultation Document** from:
   - Alnylam Pharmaceuticals

3. **Comments on the Evaluation Consultation Document from experts:**
   - Dr C Whelan– clinical expert , nominated by Alnylam Pharmaceuticals (endorsed by British Society of Heart Failure and Royal College of Physicians)
   - Professor P Hawkins – clinical expert (condition only), nominated by Alnylam Pharmaceuticals

   A 'no comment response' was submitted by NHS England

4. **Comments on the Evaluation Consultation Document received through the NICE website**

5. **Evidence Review Group critique company ECD response**

6. **Company ECD response - additional clarification questions**
   - NICE request to the company for additional clarification on their ECD response
   - Company response to NICE request and additional evidence
   - NICE request to the company for clarification on additional evidence
   - Company response to the NICE clarification on additional evidence

7. **Evidence Review Group critique additional evidence – addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Patisiran for treating hereditary transthyretin-related amyloidosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using patisiran in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of patisiran in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2018

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using patisiran in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 9 January 2019

Second evaluation committee meeting: 12 February 2019

Details of membership of the evaluation committee are given in section 6.

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1 Recommendations

1.1 Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults.

1.2 This recommendation is not intended to affect treatment with patisiran that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Hereditary transthyretin-related amyloidosis is a rare condition that severely affects the quality of life of people with the condition, their families and carers. Current treatment is supportive care.

Clinical trial evidence shows that patisiran reduces disability and increases quality of life. It may provide long-term benefits, but evidence for this is lacking.

There are uncertainties in the economic modelling. It captures some important aspects of the condition but not all the more subjective symptoms. Also, the cost effectiveness estimates for patisiran are much higher than what NICE considers acceptable for highly specialised technologies.

Patisiran reduces disability and increases quality of life and is innovative. But it does not appear to provide value for money in the context of a

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highly specialised service. Patisiran is therefore not recommended for routine funding in the NHS.

2 The condition

2.1 Hereditary transthyretin-related (hATTR) amyloidosis is an ultra-rare condition caused by inherited mutations in the TTR gene. This causes the liver to produce abnormal TTR protein, which accumulates as deposits in body tissues (amyloidosis). These deposits can disrupt the structure and damage the function of affected tissues.

2.2 Because hATTR amyloidosis can affect tissues throughout the body, people may have a range of symptoms relating to 1 or more systems. Affected systems can include the autonomic nervous system, peripheral nerves, heart, gastrointestinal system, eyes and central nervous system. The effects and complications of the condition can lead to death within 3 to 15 years of symptoms developing.

2.3 Scoring systems for evaluating hATTR amyloidosis include scores based on disability due to peripheral neuropathy, for example, the polyneuropathy disability (PND) score and the familial amyloidotic polyneuropathy (FAP) stage (Coutinho et al., 1980). The FAP stage also captures elements of autonomic neuropathy and is used in the marketing authorisation for patisiran. The description and correspondence between PND scores and FAP stages is reported in Table 1.

Table 1 Description and correspondence between PND scores and FAP stages

PND score	PND score description	FAP stage	FAP stage description
0	No impairment	**0**	No symptoms
I	Sensory disturbances, preserved walking capability	**1**	Unimpaired ambulation; mostly mild sensory and motor neuropathy in the lower limbs and autonomic neuropathy
II	Impaired walking capability but ability to walk without a stick or crutches	**2**	Assistance with ambulation needed; mostly moderate impairment

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IIIA	Walking only with the help of 1 stick or crutch		progression to the lower limbs, upper limbs and trunk
IIIB	Walking with the help of 2 sticks or crutches		
IV	Confined to a wheelchair or bedridden	**3**	Wheelchair-bound or bedridden; severe sensory and motor neuropathy of all limbs, and autonomic neuropathy
Abbreviations: FAP, familial amyloidotic polyneuropathy; PND, polyneuropathy disability			

2.4 People may mainly have symptoms of polyneuropathy or cardiomyopathy, but most patients seen in the NHS will have symptoms of both over the course of the condition. In the UK, the most common genetic mutations associated with both polyneuropathy and cardiac involvement are Val122Ile (39%), Thr60Ala (25%) and Val30Met (17%). The Val30Met mutation is associated with higher survival rates. Val122Ile is primarily associated with cardiomyopathy.

2.5 At the time of the evidence submission, there were thought to be around 150 people with hATTR amyloidosis in the UK.

2.6 Current treatment options for people with hATTR amyloidosis are limited. They mainly focus on symptom relief and supportive care including pain management, nutritional and mobility support, and lessening the effects of the condition on other organs (for example, pacemakers, arrhythmia management). There are no disease-modifying treatments available for people with hATTR amyloidosis that is being treated in the NHS. Other pharmacological treatments may be used, including diflunisal, which is sometimes used outside of its marketing authorisation to treat hATTR amyloidosis. It is contraindicated in people with cardiac impairment and those taking anticoagulants.

2.7 Liver transplant, which prevents the formation of additional amyloid deposits, might be an option for some people. However, a transplant can

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only be done early in the course of the disease, and outcomes are poor in people with cardiac involvement, so it is rarely done in England.

2.8 The National Amyloidosis Centre in London provides the only highly specialised service for people with amyloidosis and related disorders in the UK. People with hATTR amyloidosis are assessed (for overall clinical status, neuropathy progression and cardiac involvement) and followed up every 6 months at the centre, and treatment is started there. The company proposes that people would start treatment with patisiran at the centre and then, if appropriate, choose whether to continue to have treatment there or at home.

3 The technology

3.1 Patisiran (Onpattro, Alnylam) is a ribonucleic acid interference agent that suppresses transthyretin (TTR) production by the liver (including abnormal TTR). It is administered once every 3 weeks by intravenous infusion at a dose of 0.3 mg/kg. It has a marketing authorisation in the UK for treating 'hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy'.

3.2 The most common adverse reactions listed in the summary of product characteristics for patisiran include peripheral oedema, infusion-related reactions, infections, vertigo, dyspnoea, dyspepsia, erythema, arthralgia and muscle spasms. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 The price of patisiran is £7,676.45 per 10-mg vial (excluding VAT; company submission). The company has a commercial arrangement, which would apply if the technology had been recommended. This makes patisiran available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Alnylam, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Burden of disease

4.1 The patient and clinical experts explained the all-consuming nature of hereditary transthyretin-related (hATTR) amyloidosis. They highlighted that the condition affects all aspects of the lives of patients, and their families and carers. It is a multi-system condition, which has a considerable effect on patients' independence, dignity, and their ability to work, take part in family and social life, and carry out daily activities. They also highlighted that patients need a high level of care as the condition progresses. The clinical experts explained that the clinical signs of hATTR amyloidosis are heterogeneous, and can be associated with a very wide range of impairments.

4.2 The neurological deficit associated with hATTR amyloidosis progresses to the legs and the upper limbs. A survey by Amyloidosis Research Consortium UK collected information on 101 patients and 51 carers with experience of the condition. It showed that 86% of patients have numbness, tingling or pain in the lower part of their body, and 74% have muscle weakness and difficulty walking or climbing stairs. Autonomic symptoms typically include dizziness or fainting, vomiting, severe diarrhoea or constipation or both, and neurogenic bladder; 38% of patients in the survey reported having faecal or urinary incontinence that

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considerably impairs their quality of life. Symptoms may severely affect professional and social life. The patient experts explained that the condition may affect many members of the same family. Patients have often been carers for their parents, and they may also be concerned about their children developing the condition in the future.

4.3 The condition places a significant burden on family members because they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own. Carers of people with hATTR amyloidosis reported that dealing with gastrointestinal problems (especially diarrhoea), patients' mental functioning and the combination of symptoms is particularly difficult. The committee concluded that hATTR amyloidosis is a rare, serious and debilitating condition that severely affects the lives of patients, families and carers.

Unmet need

4.4 The clinical experts explained that hATTR amyloidosis is a progressive and relentless condition, and currently there are no treatments available to treat the underlying cause. The condition is usually not diagnosed immediately; there is typically a delay of 4 years from the first symptoms appearing to getting a diagnosis. As a result, at the time of diagnosis, the condition is likely to be advanced and the survival rate poor. Patient experts also explained that they have mixed experiences of symptom and disease management approaches, and that new treatments offer considerable hope to them and to their families. Patients and carers value efficacy, convenience and a low risk of side-effects. However, they are likely to accept risks if they are outweighed by treatment benefit. The clinical experts also expected that better communication and predictive testing would help to diagnose the condition earlier. Patients might be able to fully recover if a disease-modifying treatment was available. The committee recognised that there is a significant unmet need for effective treatment options for hATTR amyloidosis.

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Impact of the new technology

Clinical evidence

4.5 The committee discussed the clinical evidence available for patisiran:

- APOLLO (n=225), a randomised controlled trial that assessed the efficacy and safety of patisiran (n=148) compared with placebo (n=77) over 18 months. Results were reported overall and by subgroups (including cardiac involvement and genotype).
- A single-arm phase 2 open-label extension (OLE) study (n=27) that assessed the safety and tolerability of patisiran for up to 36 months. It captured data about patients who enrolled in a previous phase 2 open-label dose escalation study.
- Global OLE (n=211), an ongoing single-arm open-label study assessing the long-term efficacy and safety of patisiran for up to 48 months. It is capturing data on patients from APOLLO (n=186) and the phase 2 OLE (n=25), and is estimated to complete in July 2019.

The committee noted that APOLLO and Global OLE included people from the UK, and that the mutations seen in UK clinical practice were well represented in the trials (see section 0). It also noted the view of the clinical experts that the trials were generalisable to clinical practice in England. The ERG explained that, in APOLLO, there was an unexpected imbalance in dropouts between groups; a larger proportion of patients in the placebo arm stopped treatment (38%) compared with patients in the patisiran arm (7%). The clinical experts explained that they would expect the stopping rate to be higher in the placebo arm compared with the patisiran arm because adverse events linked to disease progression would be expected to be more frequent. The ERG also noted that a greater proportion of patients had cardiac involvement in the patisiran arm (61%) than the placebo arm (47%). The company highlighted that this would potentially have biased the results against

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patisiran. The committee concluded that the clinical evidence was generalisable to NHS clinical practice.

Study outcomes

4.6 The committee was aware that, in APOLLO, the primary outcome was the mean change from baseline in neurological impairment measured by the modified Neuropathy Impairment Score +7 (mNIS+7) at 18 months. The clinical experts explained that mNIS+7 is a composite measure of neurological impairment including motor, sensory and autonomic polyneuropathy assessment. A decrease in mNIS+7 score indicates an improvement in symptoms. Other outcomes collected in the trial included the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaire, assessment of serum transthyretin (TTR) levels and cardiac function (through echocardiogram and cardiac biomarkers such as troponin I and N-terminal pro-B-type natriuretic peptide [NT-proBNP]). Additional outcomes were motor strength, disability, gait speed, nutritional status, symptoms of autonomic and peripheral neuropathy, large and small nerve fibre function, grip strength, blood pressure, and ambulation (assessed using FAP stages and PND scores). Most outcomes were measured at baseline and 18 months; some were also measured at 9 months.

4.7 The committee discussed whether the outcomes captured all aspects of the condition. The clinical experts explained that hATTR amyloidosis is a systemic condition and its main features are peripheral neuropathy, and autonomic and cardiac symptoms (see sections 2.2 and 2.3). They further explained that mNIS+7 is a comprehensive measure of neurological impairment that has been specifically modified from the original NIS+7. It was modified to better characterise and quantify sensory function at multiple sites, autonomic function and nerve conduction changes associated with progression of hATTR amyloidosis, and to capture gastrointestinal dysfunction. The committee was aware that the Norfolk

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QoL-DN was developed in people with diabetes. However, the clinical experts explained that the autonomic symptoms seen in diabetes, such as gastrointestinal symptoms, are similar to those seen in hATTR amyloidosis. They further explained that NT-proBNP is a good marker of heart function and correlates with cardiac symptoms in patients with hATTR amyloidosis and that, to a certain extent, the EQ-5D-5L captures pain and fatigue. The clinical and patient experts explained that some aspects of the condition are difficult to measure because their effect on quality of life is subjective. They agreed that there was a good correlation between improvement in peripheral neuropathy and autonomic symptoms. The committee concluded that the outcomes measured in APOLLO captured most of the aspects of the condition that are important to people with hATTR amyloidosis.

APOLLO results

4.8 There was a statistically significant difference in favour of patisiran between the patisiran and placebo groups in change from baseline in mNIS+7 score. Patients in the placebo group had a worse score and patients in the patisiran group had a slightly better score (the least squares mean [LSM] difference between groups was −16.0 points at 9 months, $p<0.001$; and −34.0 points at 18 months, $p<0.001$). The treatment effect was statistically significant in all components of the mNIS+7 score and all subgroups (see section 4.5). The committee was aware that a 2-point change is considered the minimum clinically important difference (MCID), based on a consensus report from the International Peripheral Nerve Society for the original NIS score. The mean TTR reduction over 18 months was 87.8% in the patisiran group which was above the threshold of 80.0% that clinical experts advised was needed to halt or reverse neuropathic progression; it was 5.7% in the placebo group. There was a statistically significant difference in favour of patisiran between the patisiran and placebo groups in change from baseline on Norfolk QoL-DN score at 18 months; patients in the placebo

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group worsened and those in the patisiran group slightly improved (LSM difference between groups: −21.1, p<0.001). No MCID for the Norfolk QoL-DN has been reported in the literature. Cardiac outcomes were shown to improve more in the patisiran group compared with placebo at 18 months on most outcomes assessed, including left ventricular wall thickness (LSM difference between groups 0.9 mm, p=0.02) and global longitudinal strain (LSM difference between groups 1.37%, p=0.02). The difference between patisiran and placebo group in EQ-5D-5L was 0.09 points at 9 months (95% confidence interval [CI] 0.05 to 0.14) and 0.20 points (95% CI 0.15 to 0.25) at 18 months. The patient experts explained that the benefits seen in the trial translated into a marked effect on patients' lives. For example, after having patisiran, some people reported regaining a social life, not having to wear incontinence pads and being able to go to a restaurant without worrying about debilitating bowel symptoms. Another patient who has had patisiran for 4.5 years has started to walk again and is now back at work full time. The clinical experts described that a reduction of amyloid deposits in all organs has been seen in the medical imaging of some patients. This, together with the APOLLO results and other improvements in some of the patients they see in clinical practice, persuaded them that patisiran could provide compelling benefits. They added that the effect was expected to increase over the time patients have patisiran. This is because, while TTR production is supressed, the body is able to clear accumulated amyloid deposits. The committee concluded that the evidence showed that patisiran offers considerable benefit for some patients.

Long-term benefits of patisiran

4.9 The committee recalled that APOLLO collected data for up to 18 months and Global OLE was ongoing and collecting efficacy and safety data for up to 5 years. The company presented the interim data cut at 52 weeks, at which time patients had had treatment with patisiran for up to 48 months. However the ERG noted that these data should be interpreted

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with caution because they included patients who had had treatment with patisiran for different durations, depending on when they entered the study. The committee was also aware that patisiran has been available through the Early Access to Medicines Scheme and that the company intended to release data collected as part of this in the next 12 months. The committee concluded that there was no long-term clinical evidence available for patisiran, but further data were being accumulated.

Starting and stopping patisiran treatment

4.10 The marketing authorisation for patisiran states that it is indicated for treating hATTR amyloidosis at FAP stages 1 and 2. The clinical experts explained that this reflected the APOLLO trial and means that people with no symptoms would not be treated. The summary of product characteristics for patisiran does not explicitly discuss when it is appropriate to stop treatment with patisiran. The clinical experts noted that it was their experience and expectation that very few people would stop the drug. The main circumstance in which it might be appropriate to do so was if TTR reduction was not maintained. NHS England stated that it interpreted the wording of the marketing authorisation to mean that treatment should stop when the condition progress to FAP stage 3 (see Table 1). The clinical experts commented that, in the absence of explicit commissioning criteria stating otherwise, they would not want to stop treatment if the condition reached FAP stage 3 and patients were considered to still be benefitting from treatment. The committee concluded that patisiran would be started in people with FAP stages 1 and 2, and that clinicians would continue to consider using the treatment as long as patients continued to benefit.

Adverse events

4.11 The proportion of patients with adverse events in APOLLO was high (97%) in both arms, but most events were mild or moderate. Thirteen deaths occurred (n=7 patisiran; n=6 placebo) but none were causally

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related to patisiran. In patients who continued having patisiran in Global OLE, it was well tolerated for up to 48 months. The committee discussed premedication treatments (needed before having patisiran infusions) but was assured by the clinical experts that they expected risks associated with these treatments to be low. The committee concluded that the adverse events associated with patisiran are manageable.

Cost to the NHS and value for money

Company's economic model

4.12 The company presented a Markov model, in which patients could move through 12 alive health states defined by a combination of the severity of their polyneuropathy (PND score) and cardiomyopathy (NT-proBNP). Patients could transition from PND 0 to PND IV (see Table 1). Additionally, patients in each PND stage were stratified by NT-proBNP score (a value above 3,000 pg/mL denoting cardiac involvement). The model included an additional state for death. Patients could enter the model in any heath state except PND 0. The company explained the health states were based on PND and NT-proBNP scores (rather than the APOLLO primary outcome mNIS+7) because there were data relating the PND score and NT-proBNP to survival. The ERG explained that PND is not the best overall descriptor of the condition because it only captures mobility impairment (see Table 1); a model based on FAP stage would have also captured the autonomic symptoms. The company argued that PND provides a more granular assessment of the condition than FAP (because it has more stages for symptomatic patients). The clinical experts highlighted that changes in mobility are correlated with shifts in cardiac function and autonomic neuropathy so, although PND score is based on mobility impairment, it is indirectly predictive of harm and death. Despite this, the committee was concerned that the model relied on an assumed correlation between PND score and factors that patients have identified as particularly important, such as autonomic dysfunction and mortality (see section 4.7). The committee considered that although the

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model structure was broadly reasonable, it did not capture all aspects of the condition, so was unlikely to reflect the true expected cost effectiveness. It concluded that it will take this into account in its decision making.

Modelling starting and stopping patisiran treatment

4.13 The committee was aware that APOLLO (which feeds into the economic model) included a patient at FAP stage 3. Because the marketing authorisation specifies patients should have FAP stages 1or 2 when treatment starts (see section 4.10), in its preferred analysis, the ERG explored what effect removing this patient would have on the cost effectiveness. The company's model did not include a formal stopping rule so patients could continue treatment indefinitely, reflecting the marketing authorisation (see section 4.10). A discontinuation curve was applied to reflect some patients stopping over time because of, for example, adverse events. However it was assumed that patients would continue to have treatment in FAP stage 3 (corresponding to PND IV; see Table 1). The committee concluded that the starting and stopping rules applied in the model broadly reflected the way clinicians would interpret the marketing authorisation for patisiran.

Disease progression

4.14 Patients transitioned between PND health states according to 2 matrices, using a 6 month cycle. The initial matrix was derived from transitions seen in the relevant arm of APOLLO and was used for the first 3 cycles. During subsequent cycles, patients having patisiran were assumed to follow the same transition probabilities as in the first 3 cycles. However, a different approach was used to model movement of patients having best supportive care (BSC). It was assumed that they could either stay in their current health state or progress to the next worst PND state during each cycle, but not move to an improved health state. This matrix was derived from the probability that a patient's PND state worsened between baseline

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and 18 months in the placebo group of APOLLO, and the estimated probability of crossing the NT-proBNP threshold of 3,000 pg/mL or more during any given 6-month cycle. The ERG noted that the method used to convert 18-month data from APOLLO to 6-month cycles was inappropriate because there were more than 2 health states, and that this produced a small bias in favour of BSC. It also noted that it may have been informative to use a 9-month time point (for NT-proBNP). The committee concluded that the company's method of modelling of health-state transitions introduced uncertainty into the model, especially for the extrapolated period for which no long-term data exists (see section 4.9).

Health-state utilities

4.15 The company used the EQ-5D-5L utility values collected in APOLLO mapped to EQ-5D-3L (using Van Hout et al., 2012) for a regression model relating quality of life to PND score and the interaction of time by treatment. Utilities for patients having patisiran and BSC were the same at baseline, but increased every month for patients having patisiran and decreased every month for patients having BSC (utilities and regression parameters are considered confidential by the company and cannot be reported). The company capped the utility values so that they could not exceed a maximum (patisiran) or fall below a minimum (BSC) in each health state. It applied a further cap to ensure that the utilities for each health state did not exceed those for the general population in England (using data from Kind et al., 1999). The ERG considered the regression to be unreliable because it:

- excluded important parameters (such as cardiac involvement)
- included the interaction of time by treatment without the main terms (that is, time and treatment)
- chose the minimum and maximum caps arbitrarily, which would not have been needed if the model had been correctly specified.

The company explained that the results of the model had face validity

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because they reflected the decreasing quality of life in patients having BSC and the increasing quality of life in people having patisiran seen over time in APOLLO. However, the ERG explained that, without the minimum and maximum caps, the utilities reached unrealistic values. For example, over time, patients with PND II in the patisiran arm were assumed to have the same utility as patients with PND 0 (that is, no symptoms). The committee noted that a utility could vary within the same health state depending on treatment group. The company explained that this was because PND score does not reflect all aspects of the condition; people may be in the same PND state but have improved autonomic symptoms if they are taking patisiran. The committee considered that this was at odds with what it had heard from clinical experts about improvements in polyneuropathy and autonomic symptoms being correlated (see section 4.7). It questioned the reliability of the method to generate the utilities and considered that it was unlikely that someone with no symptoms would have the same utility as someone with PND II. The ERG provided a scenario analysis in which the utility values did not change over time, effectively meaning that they were the same for each health state regardless of treatment. It also explored the effect of using other sources of utilities on the cost-effectiveness estimates. In particular, it used a study by Stewart et al. (2017), which reported utilities according to FAP stage (for Val30Met mutations and 'other mutations' categories) valued using Brazilian tariffs. However, the committee was concerned that the Brazilian tariffs were very different from UK-specific tariffs, so reflected different cultural views and societal preferences. In addition, the company included a disutility for carers of 0.01 for patients with PND IV. The committee questioned whether this adequately reflected the carer burden reported in the Amyloidosis Research Consortium UK survey (see section 4.2). The committee considered that the way the company had modelled utility was highly uncertain, and that the alternative source suggested by the ERG was equally flawed. It concluded that an alternative

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modelling approach may have resulted in utility values with greater face validity.

Mortality

4.16 Mortality was modelled based on a series of hazard ratios and relied on the assumption that mortality risk increases with advancing neuropathy (PND score) and cardiac involvement (NT-proBNP). It was largely based on external data, with hazard ratios for PND score and NT-proBNP extracted from Gillmore et al. (1998) and Suhr et al. (1994) respectively, and assumed to act independently. The ERG questioned the relevance of the Suhr study because the population was not clearly defined and there was uncertainty about the survival analysis. It explained that the company's approach was convoluted, circular and uncertain but agreed there was no other existing source available. The company explained that it did not use APOLLO data to estimate mortality parameters because of the limited number of deaths. However, the ERG noted that the company did not attempt to supplement the limited APOLLO data with experts' beliefs. The clinical experts agreed with the company's approach of combining both the effect of polyneuropathy and cardiac involvement, and explained that patients usually die from cardiac complications. They noted that the hazard ratios for each PND/NT-proBNP combination were largely plausible. In its preferred analysis, the ERG assessed the impact of removing the mortality effect in patients with no cardiac involvement. The committee recognised the complexities of the company's approach and its limitations, but concluded that this approach was acceptable because of the lack of other evidence.

Resource use

4.17 The company used a Delphi approach to elicit experts' beliefs about resource use, in particular for cardiomyopathy-related costs. The ERG was concerned that the method is unlikely to have reflected the true expected cost and uncertainty. Moreover, the company included the costs

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of adverse events by assuming a constant rate of events (based on APOLLO) as well as a reduction over time (based on treatment discontinuation function; see section 4.13). The ERG considered that this was illogical because it meant that all patients would stop patisiran at the end of the time horizon and, at the same time, develop adverse events. Additionally, the committee was aware that the company proposed a homecare service for patients and noted that the costs for this were not included in its model. The committee concluded that there were some uncertainties in the company's resource use assumptions, and that it would take this into account in its decision making.

Discount rate

4.18 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, it also states that a non-reference-case rate of 1.5% for costs and health effects may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to significant irrecoverable costs. The company proposed using a discount rate of 1.5% on health effects and 3.5% on costs because it argued patisiran has shown long-term benefit and has shown the ability to halt or reverse disease progression. It accepted that patisiran was unlikely to meet the requirement that health benefits must be sustained over at least 30 years. However, it considered that this criterion unfairly penalises people with hATTR amyloidosis because they are older and so would have a life expectancy of less than 30 years even in the absence of this condition. The committee discussed the company's arguments for applying the 1.5% discount rates to health effects only and noted that:

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- Neither the NICE Reference Case nor the cited non-reference case support the use of differential discount rates (that is 1.5% for health outcome and 3.5% for costs, or vice-versa).
- The clinical experts explained that, based on response to chemotherapy in light chain amyloidosis (the most common form of systemic amyloidosis), they expected only around half of people remaining on treatment to return to what might be considered near-full heath. This is because the condition is often diagnosed at an advanced stage from which it may not be possible to return to PND 0 or FAP 0.
- Whether health benefits are sustained for 30 years is considered because cost-effectiveness analyses are particularly sensitive to the choice of discount rate when benefits are accrued over a very long time. The criterion does not therefore penalise people with hATTR amyloidosis because of the age at which they are diagnosed.
- Patisiran may be expected to provide long-term benefits but there were many remaining uncertainties that prevented the committee concluding that long-term health benefits were likely to be achieved.

The committee therefore concluded that patisiran does not meet the criteria for applying a discount rate of 1.5%. It concluded that a discount rate of 3.5% should be applied for both costs and health effects.

Other assumptions

4.19 The ERG highlighted several additional assumptions and parameters that were uncertain and that it had addressed in its preferred analysis. In particular, in the company's analysis:

- the administration and premedication costs had not been adjusted by treatment compliance
- one-off costs associated with progression of polyneuropathy had been double-counted

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- patisiran cost-savings had been double-counted by applying a treatment discontinuation function as well as a compliance rate.

  The ERG also recalculated the starting health-state distribution in the model according to the baseline data for PND and NT-proBNP in APOLLO. The committee considered the ERG's assumptions to be appropriate.

Cost-effectiveness results

4.20 The committee considered the results of the economic analysis, taking into account the company's base case and the ERG's preferred analysis and exploratory scenarios. In the company's base case, patisiran was associated with quality-adjusted life year (QALY) gains of 8.30 and an incremental cost-effectiveness ratio (ICER) above £100,000 per QALY gained compared with BSC (the ICER is considered confidential by the company and cannot be reported here). In the ERG's preferred analysis, patisiran was associated with QALY gains of 6.85 and an ICER above £100,000 per QALY gained compared with BSC. The ERG's preferred analysis:

- corrected errors in the company's model (see section 4.19)
- used a discount rate of 3.5% for costs and benefits (see section 4.18)
- recalculated starting state distribution and removed a patient with FAP stage 3 (see sections 4.19 and 4.13)
- used a utility cap for the general population based on more recent data (Ara and Brazier, 2010, rather than Kind et al., 1999)
- removed the mortality effect for lower NT-proBNP states (see section 4.16).

4.21 The committee reiterated its views on the unreliability of the utility estimates and considered an ERG's exploratory scenario in which the change of utility over time was removed (see section 4.15). This scenario led to a substantial increase in the ICER compared with the ERG's

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preferred analysis ICER. The committee concluded that the most plausible ICER was likely to lie between the ERG's preferred analysis and the scenario in which the change in utility over time was removed. Both ICERs were substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies.

Application of QALY weighting

4.22 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with patisiran, and highlighted that these were below 10 (8.30) in the company's base case, the ERG's preferred analysis (6.85) and the ERG's exploratory analysis in which utility was constant over time (3.97). The committee concluded that there was no evidence to suggest that patisiran would meet the criteria for applying a QALY weight.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.23 The committee discussed the effects of patisiran beyond its direct health benefits and the testimony of the patient experts. It understood from patient and clinical experts that all aspects of patients', families' and carers' lives are affected by the condition. It noted that there is a significant negative financial effect for families if they have to give up work to provide full-time care or need to employ professional carers. The

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patient experts explained that patisiran has changed their experience of living with hATTR amyloidosis. The committee concluded that hATTR amyloidosis affects patients beyond direct health benefits, but that quantifying this was difficult. It concluded that it was highly unlikely that the effects would be sufficient to overcome its concerns about the difference between the preferred ICER and values considered an effective use of NHS resources for highly specialised technologies.

4.24 The committee noted that hATTR amyloidosis is managed at the National Amyloidosis Centre, so no additional infrastructure or staff training will be needed to manage patisiran use in England.

Other factors

4.25 The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether the age of onset of the condition raised particular issues of equality. The committee concluded that its recommendations apply equally regardless of age or ethnicity, so a difference in disease prevalence in different age and ethnic groups does not in itself represent an equality issue.

4.26 The committee discussed the innovative nature of patisiran, noting that it is the first licensed ‘small interfering ribonucleic acid’. Therefore, its mechanism of action is distinct from all previous treatments for hATTR amyloidosis. The company considered that patisiran is a step-change in managing hATTR amyloidosis because it may dramatically improve people’s lives by slowing disease progression. The patient experts explained that having a treatment available would give people with the condition hope – both for themselves and for family members who may be affected in the future. The committee concluded that patisiran is innovative.

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Managed access

4.27 The committee reiterated the uncertainties associated with patisiran. It recalled that, although the clinical evidence might be associated with uncertainties, it was satisfied that the trial outcomes captured the main aspects of the condition, that is, peripheral neuropathy, and autonomic and cardiac symptoms (see section 4.7). It also considered that patisiran provides considerable clinical benefit. However, the committee considered that the company's model, defined by a combination of the severity of polyneuropathy (PND score) and cardiomyopathy (NT-proBNP), did not adequately capture all aspects of the condition (including autonomic symptoms) that the clinical and patient experts considered to be a major part of hATTR amyloidosis. The committee explained that this had led to an inaccurate reflection of the true expected cost effectiveness (see section 4.12). It therefore noted that further data collection, as proposed in a managed access arrangement, would not be a possible route to resolving the key uncertainties associated with patisiran because it would not address the uncertainties in the economic model. The committee acknowledged that long-term data were already being collected and would be made available in the future (see section 4.9). It concluded that patisiran could not be recommended and that a managed access arrangement would be unlikely to resolve the uncertainties.

Conclusion

4.28 The committee acknowledged that hATTR amyloidosis is an exceptionally rare condition that causes a wide variety of symptoms and impairments, and has a serious and substantial effect on the quality of life of patients, and their families and carers. It was aware that the clinical trials captured most aspects of the condition, that is, peripheral neuropathy, and autonomic and cardiac symptoms. It noted that the clinical evidence suggested that patisiran provides considerable clinical benefits. However, it considered that these clinical benefits were not appropriately represented in the economic model because the model structure was

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based on a combination of polyneuropathy and cardiomyopathy, and did not capture autonomic symptoms. In addition, the company's approach to modelling utility was highly uncertain and the resulting utility values lacked face validity. The committee considered that the most plausible ICER lies between the ERG's preferred analysis and the exploratory scenario in which utilities did not change over time. Both of these ICERs were above the range that can be considered an appropriate use of NHS resources for highly specialised technologies. It also noted that patisiran did not meet the criteria for QALY weighting to be applied, and that there remained important uncertainties within the economic model. The committee therefore did not recommend patisiran as an option for treating hATTR amyloidosis.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
December 2018

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6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Aminata Thiam
Technical Lead

Ian Watson, Ross Dent
Technical Advisers

Joanne Ekeledo
Project Manager

ISBN: [to be added at publication]

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Alnylam PHARMACEUTICALS

Highly Specialised Technologies (HST) Evaluation Programme: Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279]

Alnylam comments on the Evaluation Consultation Document

Introduction

Alnylam wishes to express our appreciation to the HST Evaluation Committee for the care, time and effort invested in appraising the evidence we have submitted in support of patisiran for treating hereditary transthyretin-related (hATTR) amyloidosis, as well as for considering the views of other stakeholders consulted for this submission. We also thank the ERG for its assessment and the multiple interactions we have had with them. We welcome the invitation to comment on the Evaluation Consultation Document (ECD), and are pleased to report that we are in broad agreement with the following sections:

- 2: The condition
- 3: The technology
- 4.1–4.4: Nature of the condition
- 4.5–4.11: Impact of the new technology

However, we believe there are specific points in the ECD where not all relevant evidence has been taken into account and/or not all interpretations of the clinical and economic evidence are reasonable, specifically in the following sections:

- 4.12–4.13, 4.14–4.17, 4.19–4.22: Cost to the NHS and value for money
- 4.23–4.24: Impact of the technology beyond direct health benefits and on the delivery of the specialised service
- 4.25–4.27: Other factors

In several instances, the ECD appears to ignore evidence stemming from the APOLLO trial – evidence that has been validated by clinicians at the National Amyloidosis Centre (NAC) who are some of the world's leading experts, evidence that formed the basis of the EMA's accelerated approval of patisiran, and evidence that led to the MHRA's decision to grant patisiran the Promising Innovating Medicine (PIM) designation. Additionally, the ECD criticises our modelling of health states as failing to explicitly incorporate some aspects of the disease, but then at the same time criticises how this was addressed elsewhere in the model based on feedback from clinical experts. This is unreasonable in our view.

Next, many of the areas of uncertainty in the ECD that underpin the overall recommendation were addressed in replies to ERG clarification questions and demonstrated to have either a limited impact on the economic results or in fact improved the results in favour of patisiran. This was described in the ERG report, our replies to ERG clarification questions, and elsewhere in the Committee

Papers. As described in our ERG replies, in several cases we took a conservative approach to modelling, to the disadvantage of patisiran, in order to be more comprehensive in our use of available evidence and expert clinical opinion we received. We believed that doing so would enhance the robustness of NICE's review and provide a greater understanding of the multi-systemic nature of hATTR amyloidosis. Yet to our disappointment, the ECD criticises some of these conservative modelling approaches and in doing so contradicts its overall negative recommendation, as alternative approaches suggested by the ERG and the Committee would have improved the cost-effectiveness in favour of patisiran. Consequently, a negative recommendation that is based on these particular arguments is contradictory and unreasonable in our view.

[redacted]

We are appreciative of NICE's timely review of patisiran and are grateful for the opportunity to provide our comments. We hope that our response provides useful additional information and clarifies misinterpretations of the evidence, and look forward to the opportunity to discuss with NHS England and with NICE our confidential commercial arrangement proposals to make patisiran available to patients.

Response to ECD

Cost to the NHS and value for money

4.12 Company's economic model

ECD: *The ERG explained that PND is not the best overall descriptor of the condition because it only captures mobility impairment (see Table 1); a model based on FAP stage would have also captured the autonomic symptoms.*

Response: We request that the Evaluation Committee reconsider this opinion from the ERG, because—contrary to the suggestion of the ERG—the FAP staging system does not capture autonomic symptoms distinctly from polyneuropathy disability. Therefore, using FAP Stages instead of PND Scores would not have improved our model's ability to capture autonomic symptoms separately from polyneuropathy

disability. On the contrary, the PND and FAP scoring systems are both predicated on mobility status. In fact, PND Scores and FAP Stages overlap to such a great degree that a mapping between these two systems has been formally defined in the literature (Table 1).

Table 1. Mapping of PND Score to FAP Stage

PND classification		**FAP stage classification**	
Score	**Symptoms**	**Stage**	**Symptoms**
0	No impairment	0	No symptoms
I	Sensory disturbances but preserved walking capability	1	Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II	Impaired walking capability but ability to walk without a stick or crutches	2	Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
IIIA	Walking only with the help of one stick or crutch		
IIIB	Walking with the help of two sticks or crutches		
IV	Confined to a wheelchair or bedridden	3	Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

FAP, familial amyloidotic polyneuropathy; PND, polyneuropathy disability.
Source: [Adams, 2013, Ando et al., 2013]

As shown in Table 1, although the FAP staging system does mention autonomic involvement, it does not separate autonomic function from the other criteria in each stage. Consequently, it cannot provide additional information on autonomic symptoms in comparison with the PND classification system. In particular, FAP Stages provide no way for a clinician to sub-classify patients on the basis of autonomic involvement independently of their mobility status. On the contrary, the FAP staging system clearly assumes that autonomic involvement correlates with mobility disability. We wish to emphasise that this essentially matches what the Committee heard about the PND scoring system from clinical experts, namely that improvements in polyneuropathy are correlated with autonomic symptoms (ECD pages 11 and 17).

Table 1 also shows that the only autonomic neuropathy referred to in the FAP classification relates to symptoms in the limbs [Ando et al., 2013]. Consequently, FAP staging does not include the gastrointestinal (GI) autonomic symptoms of hATTR amyloidosis such as diarrhoea, constipation and wasting, which clinical experts from the National Amyloidosis Centre (NAC) told us they believe to be the most important drivers of health-related quality of life (HRQoL) in this disease (as reported in our Company Submission [CS] Table D11, p 155). The patient expert statements received by the Committee for this HST evaluation also confirmed that GI-related symptoms had the greatest impact on their HRQoL; e.g., “The worst thing is the effect it has on my bowel movements. I have to be careful what I eat and have quick access to toilet facilities. This restricts where we travel and holiday types.”

Therefore, FAP Stages are no better than PND Scores at capturing the aspects of autonomic impairment that matter most to patients. Furthermore, there is no simple staging system for autonomic dysfunction.

One key reason that we used PND Score in the development of our health states is that PND Score has better discrimination in measuring changes in disease severity because it has six levels of change, whereas FAP Stage only has four levels. This difference is most notable in FAP Stage 2, which is defined as a patient who is obviously handicapped, but can still move around, although needing help. FAP Stage fails to discriminate how much assistance a patient needs with ambulation, whereas PND Score has three levels to describe these levels of disability. Clinical experts from the NAC validated our approach to model health states, including the decision to use observed PND transitions in the pivotal study, APOLLO, and stated that they preferred this approach over Pfizer's method to define FAP stages in their tafamidis submission (see CS Table D11, p 154). In addition, in its review of that appraisal, the ERG criticised the use of FAP staging.

Overall, we believe that FAP Stages are less suitable than PND Scores to capture changes in ambulatory status and neurologic impairment during the 18-month time period of APOLLO. Every other ambulatory measure evaluated in the APOLLO study (e.g., 10-metre walk test, PND Score) showed substantially more separation between patisiran and placebo over this time period than was observed with FAP Stage. This suggests that FAP Stage may not be a sufficiently sensitive instrument for measuring changes in ambulation and impairment over this time period. Therefore, using FAP Stage instead of PND Score would have made our model less clinically precise and introduced more uncertainty about the impact of patisiran on patient outcomes. Accordingly, we urge the Committee to reconsider its misinterpretation of disease staging, as basing the ECD recommendation on this would be unreasonable.

ECD: *The clinical experts highlighted that changes in mobility are correlated with shifts in cardiac function and autonomic neuropathy so, although PND score is based on mobility impairment, it is indirectly predictive of harm and death. Despite this, the committee was concerned that the model relied on an assumed correlation between PND score and factors that patients have identified as particularly important, such as autonomic dysfunction and mortality (see section 4.7). The committee considered that although the model structure was broadly reasonable, it did not capture all aspects of the condition, so was unlikely to reflect the true expected cost effectiveness.*

Response: We acknowledge that autonomic dysfunction is important to patients, but there is no single measure, and thus no single model health state, that can capture the varied manifestations of a multi-systemic disease like hATTR amyloidosis. This reality was highlighted by Professor Philip Hawkins from the NAC in his comments at the HST hearing, and was acknowledged by the ERG in their comments to the Committee. This is because autonomic involvement includes such disparate effects as GI symptoms, orthostatic hypotension, and erectile dysfunction. Bouts of constipation, diarrhoea, and faecal incontinence can be so severe as to affect patients' nutritional status and result in life-threatening wasting. Orthostatic hypotension results in dizziness and/or fainting which in turn may lead to serious

injury and hospitalization (e.g., due to falls). These effects are all clearly relevant to patients, as confirmed by the patient evidence presented at Committee; however, they also have an impact on overall HRQoL. Therefore, we believe we are justified in accommodating them in the model using EQ-5D scores, especially in light of the clear view from clinical experts that no single health state can capture the diversity of autonomic symptoms. Our rationale is that autonomic disability and any other aspects of HRQoL not explicitly defined in the PND scoring system would be encompassed by the EQ-5D data.

The fact that no single assessment exists for hATTR amyloidosis is why the APOLLO trial included multiple endpoints, including measures of autonomic neuropathy and cardiac function. Patisiran demonstrated significant benefit versus placebo on all relevant measures of autonomic dysfunction, including modified Body Mass Index (mBMI), the Composite Autonomic Symptom Score 31 (COMPASS-31), and measures of orthostasis from the mNIS+7 (i.e., postural blood pressure; see CS Section 9.6) [Adams et al., 2018]. However, the multi-systemic nature of autonomic dysfunction and measurement across several different instruments presented challenges in modelling these changes using any single unified measure. We used EQ-5D-based utilities in our model as a necessary simplification of how the varied symptoms of hATTR amyloidosis—including autonomic dysfunction—affect patients' HRQoL.

Importantly, this may underestimate the benefits of patisiran in the cost-effectiveness model, since all of these endpoints (including nutritional status/wasting) showed significant benefit in favour of patisiran versus placebo. Thus, even if there had been some way to incorporate autonomic dysfunction more directly in the model, the ICER would have been lower. In other words, the absence of a viable method to directly model dysautonomia and the need to capture this indirectly via EQ-5D-based utilities means that we took a conservative modelling approach.

The Committee's comment that our model did not capture all aspects of hATTR amyloidosis seems not to recognise that the directly measured EQ-5D data from APOLLO on which the model utilities were based would have encompassed a broad spectrum of patient-relevant symptoms of the disease.

4.14 Disease progression

ECD: *It was assumed that [patients having BSC] could either stay in their current health state or progress to the next worst PND state during each cycle, but not move to an improved health state. This matrix was derived from the probability that a patient's PND state worsened between baseline and 18 months in the placebo group of APOLLO, and the estimated probability of crossing the NT-proBNP threshold of 3,000 pg/mL or more during any given 6-month cycle. The ERG noted that the method used to convert 18-month data from APOLLO to 6-month cycles was inappropriate because there were more than 2 health states, and that this produced a small bias in favour of BSC. It also noted that it may have been informative to use a 9-month time point (for NT-proBNP). The committee concluded that the company's method of modelling of health-state transitions introduced uncertainty into the model, especially for the extrapolated period for which no long-term data exists (see section 4.9).*

Response: The model assumption that patients could not improve on BSC reflects the true clinical course of hATTR amyloidosis. Natural history studies have consistently shown that once patients start showing symptoms, their clinical state progressively worsens [Adams et al., 2015, Koike et al., 2012, Mariani et al., 2015, Ruberg et al., 2012]. Therefore, in the absence of disease-modifying therapy (i.e., with BSC), it would not be realistic to model health-state improvement. Clinical experts from the NAC validated our extrapolation method for BSC, noting that it was supported by natural history data (see CS Table D11, p 154).

We used 6-month cycles because this is the natural time period over which changes in a hATTR amyloidosis patient's course are recorded by doctors, as we were told by clinical experts from the NAC whom we consulted during model development. Prof. Hawkins' clinical expert statement for the HST evaluation confirmed, "In the UK, patients are assessed and followed-up 6 monthly at the NHS National Amyloidosis Centre …" Therefore, our use of 6-month cycles was consistent with the expert recommendation for state-transition modelling that cycle length should be short enough to represent the frequency of clinical events and interventions [Siebert et al., 2012].

The conversion from 18 months to 6 months is a challenging mathematical problem, as recognized by the ERG. In our response to the ERG (Priority Question B13), we explained that the alternate method they suggested for converting to 6-month cycles was not feasible in our case. As noted in the ECD, the ERG characterised the bias introduced by our approach as "small" and in favour of BSC—in other words, the ERG acknowledged that we took a conservative approach. It is therefore unreasonable for the ECD to use this point as justification for its recommendation.

We disagree that it would have been informative to use a 9-month time point instead, since this was not a pre-specified final endpoint assessment and would thus have been less reliable. As we explained in our response to the ERG (Priority Question B11), APOLLO was designed so that all primary, secondary, and exploratory endpoints were evaluated as differences between baseline and 18 months in the patisiran and placebo groups. Using the 18-month data (i.e., the latest time point in the study) provides the clearest idea of treatment separation over time, thus allowing us to more accurately extrapolate the treatment benefits of patisiran relative to BSC than if we had used 9-month data.

Taking all of these points into consideration, it is not justifiable to conclude that our method of modelling of health-state transitions introduced uncertainty into the model.

4.15 Health-state utilities

ECD: *The company capped the utility values so that they could not exceed a maximum (patisiran) or fall below a minimum (BSC) in each health state. It applied a further cap to ensure that the utilities for each health state did not exceed those for the general population in England (using data from Kind et al., 1999). The ERG considered the regression to be unreliable because it:*

- *excluded important parameters (such as cardiac involvement)*
- *included the interaction of time by treatment without the main terms (that is, time and treatment)*

Response: We revised the regression analysis to include the parameters the ERG requested, including the time and treatment interaction terms, and submitted the results as part of our responses to the ERG. The ECD appears to ignore this. For full details of these revisions, we encourage the Committee to review these responses. Notably, the addition of these parameters decreased the ICER relative to our own base case; in other words, our original approach was more conservative than the ERG's approach which favours patisiran. Here again, it is unreasonable for the ECD to base its recommendation on this.

ECD:

- *chose the minimum and maximum caps arbitrarily, which would not have been needed if the model had been correctly specified.*

Response: We request that the Evaluation Committee not consider the ERG's characterisation of our selection of utility caps in its decision-making, because we did not choose our maximum and minimum caps arbitrarily—instead, the selection of caps was driven by the evidence. We defined our caps on the basis of the 25th and 75th percentiles of observed EQ-5D utility data from APOLLO, stratified by treatment arm and PND score (CS, pp 129–130). The purpose for this was to avoid ceiling effects by imposing the constraint that in the long term the utilities can never cross the limits of values measured in at least half of patients in each stratum over the available 18 months of observed data. Furthermore, we consulted clinical experts from the NAC about our selection of utility caps, and they supported our approach (CS Table D11, p 155). Consequently, the ECD conclusion on this point is incorrect.

ECD: *… the ERG explained that, without the minimum and maximum caps, the utilities reached unrealistic values. For example, over time, patients with PND II in the patisiran arm were assumed to have the same utility as patients with PND 0 (that is, no symptoms).*

Response: We strongly disagree that our regression analysis (as correctly specified) generates unrealistic values. The cited objection is that PND II patients could theoretically achieve the same utility as PND 0 patients over time, which the ERG discounted as being unrealistic. This point has little practical relevance to the model results since only a very small percentage of patients accrue time in PND 0 in the model. This is evident with reference to Table 23 in our response to the ERG comments, which shows that the vast majority of patients are in PND I–IV. While it was necessary for the sake of realism to reflect the potential improvement of some patients to PND 0 (since this was observed for a number of patients in the patisiran arm of APOLLO), this applies to so few patients that it has negligible impact on the model results. Given the health-state distribution at model entry, most improvement in PND Score will be to PND I or II. Therefore, this comment in the ECD does not support the overall negative recommendation.

It is important to recognise that, as seen in other more common systemic amyloidoses—like AL amyloidosis—it *is* possible for a diseased patient with hATTR amyloidosis to reach essentially perfect health. This point was specifically raised and discussed by Prof. Hawkins from the NAC during the Committee meeting in November. The ECD states, "The clinical experts explained that, based on response to chemotherapy in light chain amyloidosis (the most common form of systemic

amyloidosis), they expected only around half of people remaining on treatment to return to what might be considered near-full heath. This is because the condition is often diagnosed at an advanced stage from which it may not be possible to return to PND 0 or FAP 0." However, while polyneuropathy and autonomic neuropathy are correlated in this disease, returning to PND 0 or FAP 0 may not be necessary to achieve comparable utility, because clinical experts from the NAC told us that (a) autonomic symptoms may progress at a different rate than PND score (a functional scale), and (b) they believe HRQoL is driven mainly by autonomic symptoms (diarrhoea, constipation, wasting) (CS Table D11, p 155). Therefore, the ECD comment implying that our model generated unrealistic utilities is misplaced because it incorrectly assumes that PND alone is driving HRQoL and hence utilities.

We note that our approach is consistent with those taken for other serious progressive diseases. For example, the possibility of overlapping utility values in patients with different PND Scores can be compared with utility valuations for the Expanded Disability Status Scale (EDSS) in models for multiple sclerosis (MS). In their NICE submission for the MS therapy Ocrevus® (ocrelizumab), Roche included utilities derived from a UK survey by Orme et al. (2007) [NICE, 2018a]. As shown in Figure 1, this survey found considerable overlap in the 95% confidence intervals (CIs) of utilities for different EDSS scores [Orme et al., 2007]. Overlapping 95% CIs were seen even for EDSS scores with such radically different levels of disability as EDSS 3 (*Moderate disability in one functional system [FS], or mild disability in three or four FS. No impairment to walking* [Multiple Sclerosis Trust, 2018]) and EDSS 6.5 (*Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting* [Multiple Sclerosis Trust, 2018]). This means that we would expect to often find an MS patient with severe walking impairment equivalent to a hATTR amyloidosis patient in PND IIIb who had a higher utility than an MS patient with unimpaired walking ability, equivalent to a hATTR patient in PND 0 or I. The observed variability in utility within an EDSS score also implies that a given patient could change their utility without changing EDSS score.

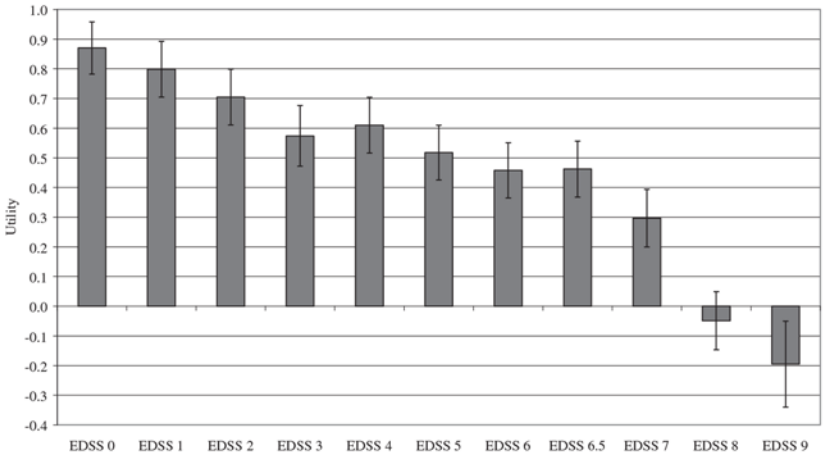

Figure 1. Utilities derived from EQ-5D by EDSS in a UK survey of patients with multiple sclerosis.

EDSS: Expanded Disability Status Scale; EQ-5D: EuroQoL 5 dimensions.
Note: Error bars show 95% confidence intervals.
Source: [Orme et al., 2007]

In rendering a positive recommendation to the Ocrevus submission, the NICE Evaluation Committee accepted the structure of the Roche economic model and concluded that it was appropriate for decision-making [NICE, 2018b]. We believe that it would be inconsistent with past NICE decisions for the Committee to disallow the way we modelled utility (in terms of how utilities behave within and across PND Scores in our model) when our method is comparable to how utility values behave in the MS model accepted by NICE.

We also disagree on principle with the interpretation that the need for utility caps means that our model was incorrectly specified or lacks face validity. In the absence of directly measured long-term utility values—a challenge often faced when modelling innovative therapies for rare diseases that are new to market—it is logical to model utilities based on the best-fit function to the observed data over the period for which utility measurements are available, then to explicitly prevent clinically implausible values over the long term by setting reasonable caps grounded in actual data. This is the approach we took, with input from clinical experts at the NAC, and given the acknowledged limitations in the currently available data, we continue to believe it to be valid.

ECD: *The committee noted that a utility could vary within the same health state depending on treatment group. The company explained that this was because PND score does not reflect all aspects of the condition; people may be in the same PND state but have improved autonomic symptoms if they are taking patisiran. The committee considered that this was at odds with what it had heard from clinical experts about improvements in polyneuropathy and autonomic symptoms being correlated (see section 4.7).*

Response: As noted above, we acknowledge that polyneuropathy and autonomic symptoms are correlated in hATTR amyloidosis. However, correlation does not imply 1-to-1 correspondence, or mean that PND Score alone captures all aspects of change in autonomic symptoms that impact patients' HRQoL and hence utilities. On the contrary, it is entirely possible for a person's autonomic symptoms and thus HRQoL to change without a change in PND score. For example, a patient's diarrhoea may improve within a certain timeframe, thereby improving their HRQoL, even if they are not able to stop using a walking stick during the same period and therefore remain in the same PND state. Furthermore, given that PND Score (or, for that matter, a FAP Stage) is not a single unique point, but rather a broad category defined on the basis of patient ability to walk, a patient could experience improvement or worsening of polyneuropathy symptoms—and thus HRQoL—without changing PND Score. We specifically posed the question of whether it was reasonable to model utility changes within a PND Score to clinical experts from the NAC during model validation as part of our original CS. We checked again that this was a valid approach in a meeting with Professors Philip Hawkins, Mary M. Reilly and Julian Gillmore from the NAC on December 19, 2018, and they stated that they continue to agree with our position.

To assess whether or not utility could improve without an improvement in PND Score, we performed a post hoc mixed-model repeated measures analysis on EQ-5D utility scores (UK valuation) from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months. As shown in Figure 2,

whereas HRQoL worsened in placebo patients who did not change PND Score, utilities steadily improved in patients taking patisiran who remained in the same PND score. Furthermore, neither of these curves was approaching a plateau by trial end, which supports our decision to include a time-dependent utility effect in the regression. These real data provide robust evidence to support change in utility over time within a PND health state and between treatment arms, demonstrating that the clinical experts from the NAC were correct in their validation of our approach, and conclusively refuting the criticism in the ECD of this aspect of our model.

Figure 2. EQ-5D utility change from baseline over time in APOLLO, mITT population who did not change PND Score from baseline

EQ-5D: EuroQoL 5 dimensions; PND: Polyneuropathy Disability; mITT: modified intent-to-treat; PND: Polyneuropathy Disability; SEM: standard error of the mean.
Source: APOLLO, post hoc analysis

We also wish to highlight that the patient expert statements reviewed by the Committee identified factors other than mobility status as the major drivers of HRQoL impairment in this disease, particularly autonomic symptoms. In fact, the main basis for the ERG's challenge of our use of PND Score to define health states is that the PND scoring system does not capture all autonomic symptoms. We are confident that the Committee will agree that it is not reasonable to, on the one hand, criticise our model for not explicitly defining health states on the basis of dimensions other than polyneuropathy disability, then on the other hand disallow our attempt to accomplish this by modelling utility variations within PND Scores (especially considering that the ERG did not find an alternative method acceptable to the Committee).

To test whether or not autonomic symptoms could improve without an improvement in PND Score, we analysed COMPASS-31 scores from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months. COMPASS-31 is a measure of patient-reported autonomic symptoms, covering six

domains: Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder, and Pupillomotor. As shown in Figure 3, whereas COMPASS-31 scores worsened (increased) in placebo patients who did not change PND Score, autonomic symptoms steadily improved (decreased) in patients taking patisiran who remained in the same PND score. This graph conclusively demonstrates that patients in the same PND Score do indeed experience ongoing improvement in autonomic symptoms over time if they are taking patisiran.

Figure 3. COMPASS-31 change from baseline over time in APOLLO, mITT population who did not change PND Score from baseline

COMPASS-31: Composite Autonomic Symptom Score 31; LS: least square; mITT: modified intent-to-treat; PND: Polyneuropathy Disability; SEM: standard error of the mean.
Note: higher scores indicate worse quality of life.
Source: APOLLO, post hoc analysis

Given the importance of autonomic symptoms to HRQoL as highlighted by the NAC experts, Figure 3 also supplies a mechanistic explanation of why we observe that utilities do in fact vary within the same PND Score (as seen in Figure 2), and also why it is entirely plausible that patients with different PND Score could have the same utility.

However, we would also like to point out that utility scores in the model are not fully independent of PND Score but instead are based on EQ-5D data gathered in APOLLO and stratified by PND Score. Thus, the influence of polyneuropathy on utilities is explicitly included in the model, with inclusion of an additional factor (i.e., time-varying change in utility score) to reflect the fact that EQ-5D-based utility scores are observed to change within a given PND Score. Therefore, there is no justification for the Committee's conclusion that the way we modelled utility was unreliable and highly uncertain; on the contrary, it is grounded in observed data and consistent with clinical expert opinion and patient testimony. The ECD conclusions on this point are unreasonable in our view.

ECD: *It questioned the reliability of the method to generate the utilities and considered that it was unlikely that someone with no symptoms would have the same utility as someone with PND II.*

Response: Above we have addressed the criticisms regarding the reliability of our method for generating utilities. Here we wish to reiterate that very few patients will improve to PND 0, and so, as explained above, the apparent issue relating to utilities in PND 0 has no meaningful impact on the model results. We should also emphasise that just because a patient in PND 0 may have no polyneuropathy impairment does not mean that they are disease-free or have no symptoms of any kind. As in the FAP staging system, patients with stage 0 disease already have evidence of amyloid deposits [Ando et al., 2013], so it is plausible that some level of impairment and thus impact on utility could already be detected. Consequently, this comment in the ECD lacks validity and does not support the overall negative recommendation for patisiran.

ECD: *The ERG provided a scenario analysis in which the utility values did not change over time, effectively meaning that they were the same for each health state regardless of treatment.*

Response: This scenario analysis from the ERG should not be considered by the Committee, because there should be no disagreement that utility values and HRQoL can change over time in the 18-month study period—this is empirically true, as was observed in the overall APOLLO trial population (i.e., modified intent-to-treat), consistent with the results for the subgroup of patients with no change in PND Score from baseline shown in Figure 2 and Figure 3. Taking into account all of the evidence presented above, it is clearly unrealistic to model a scenario in which utility values are static within each model health state. Furthermore, we specifically discussed this question with the clinical experts from the NAC at our meeting on December 19, 2018, and they continue to support our position.

To further illustrate that (a) HRQoL changes over time within a PND Score, (b) HRQoL is consistently better in patients receiving patisiran than in those receiving placebo, and (c) the HRQoL difference between the two treatment arms continues to diverge over time, we analysed results from APOLLO on the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire for the subset of patients who remained in the same PND Score from baseline to 18 months. Change from baseline on the Norfolk QoL-DN was the highest-ranked secondary endpoint in the protocol-specified hierarchical order for statistical testing in APOLLO [Adams et al., 2018]. The Norfolk QoL-DN is a validated measure of HRQoL for hATTR amyloidosis, which captures patients' assessments of neuropathy symptoms as they relate to five HRQoL domains: physical functioning/large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy [Vinik et al., 2014]. Figure 4 shows that HRQoL improves in patients on patisiran and worsens in those taking placebo even within a given PND Score.

Figure 4. Norfolk QoL-DN change from baseline to 18 months in APOLLO, mITT population who did not change PND Score from baseline

LS: least square; mITT: modified intent-to-treat; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; SEM: standard error of the mean.
Note: higher scores indicate worse quality of life.
Source: APOLLO, post hoc analysis

It is crucial to understand that a given PND Score (or, for that matter, a FAP Stage) is not a single unique point, but rather a broad category defined on the basis of patient ability to walk. Therefore, staying in a PND Score does not mean that the disease is stable—not only could autonomic symptoms change, but even the severity of polyneuropathy symptoms could change within a PND Score before having a large enough impact on functioning to require reclassification to the next higher or lower PND Score. We raised this question with clinical experts from the NAC during model development and again at our December meeting with Profs. Hawkins, Reilly and Gillmore, and these experts consistently supported our approach.

The fact that disability can change without necessarily triggering a change in PND Score can also be seen by looking at the R-ODS scores from APOLLO for the subset of patients who remained in the same PND Score from baseline to 18 months (Figure 5). R-ODS measures overall disability in terms of activity and social participation limitation [Regnault et al., 2017]. The graph shows that R-ODS was stable in the patisiran arm, which is not unexpected since both PND Score and R-ODS assess disability, and by definition this is the subgroup of patients without change in PND Score. What is striking in Figure 5, however, is that R-ODS declined steadily in the placebo arm, indicating worsening disability, *even though this is a subgroup of patients who remained in the same PND Score from baseline*. This confirms that HRQoL—even HRQoL linked specifically to disability—can vary without being detectable by a change in PND Score.

[redacted]

Figure 5. R-ODS change from baseline over time in APOLLO, mITT population who did not change PND Score from baseline

LS: least square; mITT: modified intent-to-treat; PND: Polyneuropathy Disability; R-ODS: Rasch-built Overall Disability Scale; SEM: standard error of the mean.
Note: higher scores indicate better quality of life.
Source: APOLLO, post hoc analysis

Given the continuing separation of the utilities and other HRQoL measures between the patisiran and placebo arms shown in Figure 2 to Figure 5, with patients on patisiran always faring better over time than patients on placebo, it is clearly reasonable to extrapolate these observed effects into the post-trial period (i.e., after 18 months) using regression analysis as we have done.

ECD: *[The ERG] used a study by Stewart et al. (2017), which reported utilities according to FAP stage (for Val30Met mutations and 'other mutations' categories) valued using Brazilian tariffs. However, the committee was concerned that the Brazilian tariffs were very different from UK-specific tariffs, so reflected different cultural views and societal preferences.*

Response: We agree with the Committee that the ERG's scenario using the Brazilian tariff data is not valid to consider in the context of this HST submission. Not only are the cultural views and societal preferences from the Brazilian study not representative of the UK, but also the distribution of TTR mutations (mostly V30M) and preferences of the patients are likely to be different and thus not relevant to the UK.

ECD: *the company included a disutility for carers of 0.01 for patients with PND IV. The committee questioned whether this adequately reflected the carer burden reported in the Amyloidosis Research Consortium UK survey (see section 4.2).*

Response: We acknowledge there may be underestimation of the burden experienced by caregivers, but more fully incorporating these effects may decrease

the ICER for patisiran relative to BSC. Thus, our approach was likely conservative. We have addressed this concern in the revised analysis described on page 20, which did indeed yield more favourable results (i.e., a lower ICER) for patisiran.

ECD: *The committee considered that the way the company had modelled utility was highly uncertain, and that the alternative source suggested by the ERG was equally flawed. It concluded that an alternative modelling approach may have resulted in utility values with greater face validity.*

Response: We agree with the Committee that the ERG's approach to utilities was flawed, but trust that we have demonstrated in the preceding responses that our method is reasonable, as it reflects:

- Actual utility data from APOLLO
- The clinical reality that HRQoL changes within a given PND Score over time, as supported by a range of different measures
- The continuing divergence of utilities and other HRQoL measures between the patisiran and placebo arms over the entire course of the APOLLO trial, representing ongoing improvement in patients taking patisiran and worsening in patients on placebo
- Lower and upper limit values applied after regression analysis in the model in order to ensure that the benefits in each treatment arm will not become unreasonably low or high over time

Importantly, all of these aspects of our methodology were validated with clinical experts from the NAC during model development for the CS. We discussed specific objections from the ECD during our December meeting with Profs. Hawkins, Reilly and Gillmore, and they supported our position. Furthermore, as explained above, our approach to utilities is consistent with the Roche Ocrevus submission, which NICE accepted.

Taking all of these points into account, it is evidently not justifiable to render a negative decision on patisiran based on criticisms of our approach to utilities. It also does not appear to be reasonable to hypothesise that an alternative approach may have provided greater face validity without specifying what said approach would entail, especially since even the ERG was unable to offer a more satisfactory alternative. Therefore, we urge the Committee to revisit their conclusions about our approach to utilities and take these arguments into account in a re-evaluation of patisiran.

4.16 Mortality

ECD: *The ERG questioned the relevance of the Suhr study because the population was not clearly defined and there was uncertainty about the survival analysis. … The committee recognised the complexities of the company's approach and its limitations but concluded that this approach was acceptable because of the lack of other evidence.*

Response: We agree with the ERG that uncertainty is introduced by use of the Suhr study [Suhr et al., 1994]. This is the only paper available in the literature that describes the relationship between the polyneuropathy in this disease and mortality,

and the clinical experts from the NAC we consulted on model methodology considered this appropriate in the absence of other sources. They also agreed that in spite that in the UK the mortality is mainly due to cardiac symptoms, it is appropriate to include mortality associated to PND Score in the model even with the significant limitations of the Suhr data (see CS Table D11, p 154). The introduction of the Suhr data may overestimate the mortality associated to PND Scores in the UK and thus underestimate the cost-effectiveness of patisiran, meaning that the ICER is likely to be lower than the result of the base-case model in the CS. Profs. Hawkins, Reilly and Gillmore confirmed this hypothesis at a December 2018 meeting at the NAC. To address the ERG's concerns, we removed all mortality due to polyneuropathy (i.e., not using the data from Suhr et al. [1994]). As reported on page 22 below, implementing this change yields a significant reduction in the ICER compared with the result of the base-case model in the CS.

A multivariate analysis using data from APOLLO to model the effect of different degrees of polyneuropathy on survival was planned, but was not conducted due to the low number of deaths in APOLLO. In the absence of other data sources at the time of submission, it was not possible to model the effects (or even thresholds) of polyneuropathy or autonomic function on survival. Since in APOLLO patisiran had uniformly positive impacts on autonomic symptoms and wasting, which we did not model as survival gains in the model for the reasons stated above, our method clearly underestimated the cost-effectiveness of patisiran. It is unreasonable for the ECD to justify its conclusions based on this point.

4.17 Resource use

ECD: *The company used a Delphi approach to elicit experts' beliefs about resource use, in particular for cardiomyopathy-related costs. The ERG was concerned that the method is unlikely to have reflected the true expected cost and uncertainty. Moreover, the company included the costs of adverse events by assuming a constant rate of events (based on APOLLO) as well as a reduction over time (based on treatment discontinuation function; see section 4.13). The ERG considered that this was illogical because it meant that all patients would stop patisiran at the end of the time horizon and, at the same time, develop adverse events. Additionally, the committee was aware that the company proposed a homecare service for patients and noted that the costs for this were not included in its model. The committee concluded that there were some uncertainties in the company's resource use assumptions, and that it would take this into account in its decision making.*

Response: We acknowledge there were limitations in our ability to define resource use, but wish to emphasise that the information we incorporated in the model was derived from asking some of the world's leading experts in the management of hATTR amyloidosis, who are thus uniquely well placed to advise on resource use in this condition. We presented multiple scenarios in addressing healthcare resource utilization in our responses to the ERG clarification questions and none of them has a meaningful impact on the ICER presented in the base-case model in the CS. In our view, it is therefore unreasonable for the ECD to justify its conclusion based on this point.

4.18 Discount rate

ECD: *The committee therefore concluded that patisiran does not meet the criteria for applying a discount rate of 1.5%. It concluded that a discount rate of 3.5% should be applied for both costs and health effects.*

Response: Although we disagree that applying the same discount rate to costs and health effect because it discriminates against diseases affecting middle age and elderly patients, we have revised our final proposed model accordingly.

4.19 Other assumptions

ECD: *The ERG highlighted several additional assumptions and parameters that were uncertain and that it had addressed in its preferred analysis. In particular, in the company's analysis:*

- *the administration and premedication costs had not been adjusted by treatment compliance*
- *one-off costs associated with progression of polyneuropathy had been double-counted*
- *patisiran cost-savings had been double-counted by applying a treatment discontinuation function as well as a compliance rate. The ERG also recalculated the starting health-state distribution in the model according to the baseline data for PND and NT-proBNP in APOLLO. The committee considered the ERG's assumptions to be appropriate.*

Response: We previously addressed these concerns in our response to the ERG comments. As confirmed by the ERG, implementing these changes did not substantially alter the ICERs:

- Base-case: [redacted]
- Correction of double-counting of one-off costs: [redacted]
- Correction of double-counting of patisiran cost savings: [redacted]

4.21 Cost-effectiveness results

ECD: *The committee reiterated its views on the unreliability of the utility estimates and considered an ERG's exploratory scenario in which the change of utility over time was removed (see section 4.15). This scenario led to a substantial increase in the ICER compared with the ERG's preferred analysis ICER. The committee concluded that the most plausible ICER was likely to lie between the ERG's preferred analysis and the scenario in which the change in utility over time was removed. Both ICERs were substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies.*

Response: We categorically disagree with this conclusion, as it is based on a scenario that (a) is refuted by observed data from APOLLO, (b) conflicts with NAC clinical expert opinion, and (c) contradicts other arguments made by the Committee in the ECD. Regarding point (c), in Section 4.15 of the ECD the Evaluation Committee judged the ERG's approach to utilities to be flawed, and thus it is not reasonable to consider the ERG's exploratory scenario in which the change of utility over time within a given PND Score was removed. This scenario is clinically implausible because it implies that PND Score alone is able to capture all relevant

aspects of hATTR amyloidosis patients' HRQoL, and thus that utilities would not change over time within a given PND Score. As shown in Figure 2, this implication is demonstrably incorrect, refuted by data from the largest trial ever performed in this disease state. This scenario is also incompatible with expert clinical opinion from Profs. Hawkins, Reilly, and Gillmore, who are among the world's leading experts in this disease. It would also be inconsistent to criticise our use of PND Score to define health states because this system does not capture all aspects of the disease (including autonomic dysfunction), but then penalise us for attempting to address this issue by capturing the broad spectrum of symptoms via changing utilities within a given PND Score. We therefore request that the Committee not consider this exploratory scenario among the possible range of ICER values. Doing so would conflict with observed clinical evidence and expert clinical opinion, and would therefore be unreasonable in our view.

4.22 Application of QALY weighting

ECD: *[The Committee] understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with patisiran, and highlighted that these were below 10 (8.30) in the company's base case, the ERG's preferred analysis (6.85) and the ERG's exploratory analysis in which utility was constant over time (3.97). The committee concluded that there was no evidence to suggest that patisiran would meet the criteria for applying a QALY weight.*

Response: The potential QALY gain for any therapy for hATTR amyloidosis is inherently limited by the fact that this disease predominantly strikes the elderly. The median age at symptom onset for hATTR amyloidosis patients in the UK with the underlying Thr60Ala mutation is 63 years (range: 45–78 years) [Sattianayagam et al., 2012]; with the Val122Ile mutation is 77 years (range: 47–92 years); and generally for non-Val122Ile mutations is 66 years (range: 41–82) years [Gillmore et al., 2017]. To use the same criteria for QALY gains in hATTR amyloidosis as for diseases of younger patients would discriminate against the elderly. As previously noted, the ERG's exploratory analysis in which utility was constant over time is based on a faulty assumption, disproved by actual data from APOLLO, so the calculated QALY gain of 3.97 should be disregarded. Therefore, the remaining QALY-gain estimates are quite close (8.30) to the threshold of 10 for applying QALY weighting. Moreover, as explained throughout this response, many aspects of the modelling approach we adopted were conservative (i.e., to the disadvantage of patisiran). In addition, much of the clinical benefit observed in the APOLLO trial cannot easily be modelled, especially with regard to the benefit of patisiran on the main determinant of HRQoL in this disease, namely autonomic functioning. Such limitations are common to cost-effectiveness analyses for specialised medicines for very rare diseases. In the case of patisiran, the QALY-gain estimates calculated in our base-case analysis and the ERG's analysis are not only close to the threshold for weighting, but they are also undoubtedly conservative. Therefore, it is probable that the 'true' QALY value meets or exceeds the threshold for weighting. Given the equity issue regarding the elderly patient population, we urge reappraisal of the eligibility of patisiran for QALY weighting.

4.25 Other factors

ECD: *The committee noted the potential equality issue raised by clinical experts and the company, and recognised that specific mutations were more common in some ethnic groups in the UK. It also considered whether the age of onset of the condition raised particular issues of equality. The committee concluded that its recommendations apply equally regardless of age or ethnicity, so a difference in disease prevalence in different age and ethnic groups does not in itself represent an equality issue.*

Response: Although the recommendations do not differ by age, the application of the same threshold for QALY weighting for hATTR amyloidosis as for other conditions does raise equity issues, as described in our previous response, because it gives preference to therapies for younger patients.

In addition, while the recommendations of the Committee would apply without regard to ethnicity, the higher prevalence of specific hATTR amyloidosis-associated mutations in some historically disadvantaged groups (e.g., Afro-Caribbean and Irish) could raise equality concerns relating to disproportionate harm on these communities if access to patisiran is not provided, when considered alongside other therapies for orphan indications that have been recommended by NICE.

4.27 Managed access

ECD: *the committee considered that the company's model, defined by a combination of the severity of polyneuropathy (PND score) and cardiomyopathy (NT-proBNP), did not adequately capture all aspects of the condition (including autonomic symptoms) that the clinical and patient experts considered to be a major part of hATTR amyloidosis. The committee explained that this had led to an inaccurate reflection of the true expected cost effectiveness (see section 4.12).*

Response: Our model explicitly included a measure of polyneuropathy (PND Score) and cardiomyopathy (NT-ProBNP). As no single measure exists to capture autonomic dysfunction, it was not feasible to explicitly model this. However, we did capture the impact of autonomic dysfunction on HRQoL by use of EQ-5D-based utility scores directly collected in APOLLO. As previously explained, all of the HRQoL measures in the trial showed divergence over time between the patisiran and placebo arms. Thus, while we recognise (as confirmed by clinical experts from the NAC) that autonomic dysfunction has an impact on mortality, by not including this mortality source in our modelling of survival benefits we are actually underestimating the benefits and cost-effectiveness of patisiran. Consequently, this ECD criticism does not substantiate the overall negative recommendation.

ECD: *It therefore noted that further data collection, as proposed in a managed access arrangement, would not be a possible route to resolving the key uncertainties associated with patisiran because it would not address the uncertainties in the economic model.*

Response: We strongly disagree with this conclusion. In criticising our method for modelling health-state transitions (ECD Section 4.14), the Committee highlighted that uncertainty applied "especially for the extrapolated period for which no long-term

data exists". This statement is incompatible with the suggestion that long-term data would be unhelpful to addressing uncertainties in the model. On the contrary, additional data, especially long-term data, are going to be extremely important in defining the true value of patisiran.

We note that in his expert statement to the Committee, Prof. Hawkins reported, "The experience of my colleagues at the NAC treating patients through compassionate access (over one year) and Early Access to Medicine Schemes has been extremely favourable. Remarkable clinically significant improvements of well-being and function have occurred in a majority of cases, including regaining the ability to walk unaided." This statement makes clear that long-term data gathered in clinical practice are going to be crucial in resolving remaining uncertainties associated with patisiran, providing yet another incentive to expand patient access to this therapy. The outright rejection of any value from any additional evidence or long-term data, especially from the EAMS program, directly conflicts with current clinical experience and is unreasonable. We urge the Committee to reconsider.

4.28 Conclusion

ECD: *[The Committee] noted that the clinical evidence suggested that patisiran provides considerable clinical benefits. However, it considered that these clinical benefits were not appropriately represented in the economic model because the model structure was based on a combination of polyneuropathy and cardiomyopathy, and did not capture autonomic symptoms. In addition, the company's approach to modelling utility was highly uncertain and the resulting utility values lacked face validity. The committee considered that the most plausible ICER lies between the ERG's preferred analysis and the exploratory scenario in which utilities did not change over time. Both of these ICERs were above the range that can be considered an appropriate use of NHS resources for highly specialised technologies. It also noted that patisiran did not meet the criteria for QALY weighting to be applied, and that there remained important uncertainties within the economic model. The committee therefore did not recommend patisiran as an option for treating hATTR amyloidosis.*

Response: Given the clarifications provided above regarding the appropriateness of our approach to modelling utility, we feel justified in requesting a reconsideration of the validity of our approach, and respectfully request a reappraisal of this decision. In support of this request, we reconstructed the ERG's preferred model and also implemented additional changes recommended by the ERG in order to arrive at a new base case.

Reconstruction of ERG-preferred analysis

Although we have responded above to a limited number of specific criticisms of our model with which we disagree, the ERG suggested several model changes that we consider to be important corrections or valid alternate approaches. To obtain results consistent with the ERG's preferred analysis, we implemented the same changes to the model that the ERG made, as follows:

1. Correction of errors
    a. Patisiran administration and premedication costs were down-weighted by relative dose intensity (RDI)

   b. One-off costs were removed from the analysis for all PND scores
   c. The cumulative probability of being on treatment was set equal to 1.0 over the entire time horizon (i.e., the time-to-treatment-discontinuation function was removed from the model)
2. Equal discount rates were applied for health outcomes and costs. In line with the NICE guide to the methods of technology appraisal [NICE, 2013], discount rates for health outcomes and costs were set equal to 3.5%.
3. Recalculation of initial distribution by PND and NT-proBNP score
4. Use of general population HRQoL from Ara & Brazier [2010]
5. Adjustment of calculations to estimate mortality risk by PND stage for low NT-proBNP states. Within this analysis, the inflation of mortality risk due to NT-proBNP (using a hazard ratio from Gillmore et al. [2017]) was removed from the analysis of survival by PND stage using data from Suhr et al. [1994] for the low NT-proBNP model health states.

Definition of base case

In order to obtain a plausible range of ICERs consistent with the ERG's approach, we constructed two scenarios of the base-case model, as follows:

Scenario A: ERG approach + two additional changes recommended by the ERG

Change #1: In response to ERG questions we presented a regression model including all terms (i.e., treatment and time as separate terms and NT-proBNP). In our answer we explained that the goodness of fit provided by this full model was poorer than that provided by our base-case model. However, the ERG maintained their criticism and the Committee recognised this. For this reason, we included here the full EQ-5D regression into the cost-effectiveness model.

Change #2: To address the Committee's questioning of the appropriateness of the caregiver disutility used in our originally submitted model, we updated caregiver disutilities considering the data in Akcea Therapeutics' HST submission for inotersen. Akcea presented the disutilities shown in Table 2, assuming that each patient would have two full-time caregivers in all stages of the disease [NICE, 2018c]. While the ERG accepted the unit disutilities per caregiver, they rejected the assumption that patients would have two caregivers, and instead considered one full-time caregiver for each patient in all stages of the disease. Accordingly, we also assumed here carer disutilities for one caregiver per patient.

Table 2. Caregiver disutilities in the NICE HST submission for inotersen.

Health state	EQ-5D-3L disutility per carer	Total disutility applied in model (2× carers)	Note
Stage 1	-0.0025	-0.0050	Average of EDSS 0–3.0 (no impairment to walking)
Stage 2	-0.0275	-0.0550	Average of EDSS 3.5–7.0 (walking assistance)
Stage 3	-0.125	-0.2500	Average of EDSS 7.5–9.5 (wheelchair or bedridden)

EDSS: Expanded Disability Status Scale; EQ-5D-3L: EuroQoL 5 dimensions, 3-level questionnaire.

Source: [NICE, 2018c]

Applying the model changes described above, we obtained the results shown in Table 3, yielding an ICER of [redacted] (discounted). This ICER includes our approved simple PAS.

Table 3. Results of cost-effectiveness model using ERG approach + all regression terms + revised carer disutilities, with simple PAS.

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference						
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; Disc: discounted; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Scenario B: ERG approach + all regression terms + revised carer disutilities + removal of mortality associated with PND, with simple PAS

The ERG criticised the estimation of mortality by PND because of the weakness of the source [Suhr et al., 1994] and the complexity of the method. As a part of their scenario analysis the ERG considered a case in which PND mortality was removed from the model. This scenario is not entirely implausible, since most patients with hATTR amyloidosis die from cardiac complications or wasting [Carvalho et al., 2015], rather than from polyneuropathy. Accordingly, we constructed a model scenario without PND mortality. The results of this scenario are presented in Table 4. The ICER of [redacted] (discounted) includes the approved simple PAS.

Table 4. Results of cost-effectiveness model using ERG approach + all regression terms + revised carer disutilities + no PND mortality, with simple PAS.

	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference						
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Undiscounted		Discounted	
ICER	**Cost/LY**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**
Patisiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; Disc: discounted; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

We can conclude that, prior to the application of any confidential commercial arrangement agreed with NHS England, the base case ICER for patisiran compared with BSC probably somewhere between these two estimates from the two scenarios above, namely [redacted].

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted] These proposals were previously discussed with various stakeholders and we welcome the opportunity to discuss further with NHS England and NICE at the earliest opportunity.

Table 5. Impact of commercial arrangements on the ICERs from the revised base cases shown above.

Commercial arrangement	Impact on ICER vs model using ERG approach +		Mean impact*
	All terms + revised carer disutilities	Previous scenario + No PND mortality	
[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; PND: polyneuropathy disability.
*Average of impact vs. both model scenarios.

Conclusion

[redacted]

We hope our response to the ECD consultation is helpful in advancing a thorough review of this important new medicine, and thank NICE once again for the opportunity to comment.

Kindest regards

Anant Murthy, PhD
Vice President, Market Access
Alnylam Pharmaceuticals

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Highly Specialised Technology
Patisiran for treating hereditary transthyretin amyloidosis [ID1279]
Evaluation consultation document

Dr Carol Whelan's response on behalf of British Society of Heart Failure and Royal College of Physicians, January 2019.

Within this evaluation document, the committee has accurately described the condition, hereditary transthyretin-related amyloidosis, its burden on patients and their carers and the unmet need of this disease. The increasing burden as the disease progresses on patients and importantly, their family members who provide care, in terms of independence, dignity, ability to work and carry out daily activities is described. There is no treatment at present. With best supportive care, the disease progresses with the patient ultimately bedbound.

The committee concludes that clinical trial evidence demonstrates that patisiran reduces disability and increases quality of life. It may provide long-term benefits but evidence for this lacking. It also concludes that there are uncertainties in the economic modelling as although the important aspects of the condition are captured, not all more subjective symptoms are covered. The cost effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies. Patisiran is innovative but does not appear to provide value for money and therefore is not recommended for routine funding in the NHS.

- Has all of the relevant evidence been taken into account?

The committee discussed and took into account relevant evidence with respect to patisiran, namely APOLLO comparing patisiran with placebo, a single arm phase 2 open label extension (OLE) study and the ongoing global OLE study. These studies are relevant to a UK population. The clinical effectiveness of patisiran is demonstrated in the APOLLO study. Long term data are being accumulated in the OLE study.

- Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

These summaries are reasonable interpretations.
A mean TTR reduction of 87.8% was seen with Patisiran. A threshold for TTR knockdown at 80% for clinical effectiveness is discussed. It should be noted that this percentage has not been validated in TTR amyloidosis, although it is accepted that the higher the knockdown in all types of amyloidosis, the higher the percentage of patients whom are likely to benefit in terms of halting or reversing progression of disease. The turnover and production of TTR varies from patient to patient so some may derive benefit from a knockdown lower than 80% while other patients may require a much higher level of knockdown to gain the same benefit.

The company's base case as well as the ERG's analysis, are described. In both scenarios, patisiran was associated with an ICER above £100,000 per QALY gained (which NICE considers acceptable).

- Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

I agree that these recommendations are sound and a suitable basis for guidance to NHS England at present.

C Whelan

January 2019

I would like address two points:

1) Potential for efficacy of patisiran in the longer term:

My expectation is that patisiran treatment, through substantially reducing the supply of the ATTR amyloid precursor protein (i.e. plasma TTR) by more than 80%, will lead to sustained benefit and likely further improvement in the function of organs and tissues affected by ATTR.

This expectation is based on:

1. Experience in the National Amyloidosis Centre of thousands of patients with other types of amyloidosis, most notably more than 5000 patients with AL amyloidosis in whom amyloid precursor protein (light chain) knock-down through chemotherapy has been associated with hugely improved long term survival, ongoing gradual regression of amyloid, and ongoing gradual improvement in amyloidotic organ function.

The rationale / plausibility for sustained benefit of patisiran in ATTR amyloidosis is completely analogous with knock-down treatments of all other types of amyloidosis. There is a very robust and consistent relationship between amyloid precursor protein supply and the course of amyloid deposition in all types.

2. Data from Alnylam's longer term studies of patisiran, which suggest that the benefit of patisiran is maintained and prolonged.

3. Very positive experience in the National Amyloidosis Centre among patients receiving patisiran via the compassionate access programme and EAMS. We have treated 30 patients with hereditary ATTR amyloidosis, ten for over one year. The treatment has been safe, and several of the ten patients who have been treated for one year have reported very significant improvements in mobility and nerve symptoms. The single patient who was wheelchair bound at the start of treatment is now able to walk with stick.

[redacted]

Figure: Serial Tc-DPD scans in a patient with hATTR amyloidosis with cardiac involvement, one year apart following treatment with patisiran via UK compassionate scheme. [redacted]

[redacted]

2) Comments re PND score:

There has been some misconception regarding the correlation of the PND score value and other clinical measurements relating to amyloid associated organ dysfunction. Patients may improve very significantly on treatment whilst remaining within a particular PND grade since the latter is a useful but quite crude measure and does not capture many elements in the disease that are important to patients, particularly autonomic dysfunction, which causes many of the most unpleasant and disabling symptoms (eg incontinence).

Alnylam's analysis shows that patients who remained within the same PND score on patisiran did experience a significant benefit in a wide range of measures versus those on placebo (EQ5D, Norfolk, Compass and RODS). It is clear then that patisiran treatment can improve symptoms over a relatively short 18 month period whilst not being associated with a change in PND score.

Philip Hawkins 7 Jan 2019

Comments on the ECD Received from the Public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	[redacted]
Location	
Conflict	[redacted]
Notes	

Comments on the ACD:

[redacted] would like to thank the committee for the opportunity to submit comments on the Evaluation Consultation Document (ECD) for patisiran for treating hereditary transthyretin-related amyloidosis (hATTR).

We welcome the committees recognition of the high level of unmet need for patients in the UK suffering from hATTR and challenges presented by its ultra-rare condition status. Further, [redacted] appreciates the clarity provided on the economic model structure appropriate to hATTR disease, discount rate, adverse events, and utilities.

However, [redacted] wishes to challenge some elements of the committees comments in the ECD. These include:

1 Long-term benefit of patisiran, with particular note made of the role of TTR reduction as a predictor of long-term benefit;

2 Clarity of reporting of NICE decision process in some instances

3 Treatment stopping rules applied to patients in different FAP stages of disease;

4 Treatment discontinuation curve adopted;

5 The value or costs associated with patient preference

<u>Long term benefit of patisiran</u>

In Section 4.8 of the ECD, the committee concludes that the evidence shows that patisiran offers considerable benefit for some patients. This is based on two main arguments:

1. Expectation of an increase over time in clinical benefit of patisiran, evidence for which includes:

o A patient who has had patisiran for 4.5 years beginning to walk and work full time again;

o Other improvements observed in some patients in clinical practice;

o Medical images showing reduction of amyloid deposits in all organs for some patients.

2. Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study, from which the committee has concluded:

- A TTR reduction of >80% represents a threshold above which
- Patisiran is likely to have surpassed this threshold

[redacted] contests the appropriateness and accuracy of both of these judgements

Please see comment 8 'Expectation of an increase over time in clinical benefit of patisiran' for response to the first issue and comment 9 'Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study ' for response to the second.

Treatment stopping rule

The ECD makes reference to the fact that the economic model did not include a formal stopping rule, reflecting the possibility of patients receiving patisiran indefinitely. However, patisirans marketing authorisation is for patients with hATTR amyloidosis at FAP stages 1 and 2.

Clinical experts at the committee meeting have commented that it is possible that a patient benefitting from patisiran and their clinician would not want to stop treatment when that patient entered Stage 3. However, NHS England states that the wording of the marketing authorising was interpreted to mean that when patients progress to FAP stage 3, treatment should stop.

The Summary of Product Characteristics is explicit about the license of the product:

Onpattro [patisiran] is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy (European Medicines Agency, 2018)

We are mindful that it is NICE remit to assess patisiran within its marketing authorisation as per the NICE scope, and have found no precedent where NICE have extended their remit to assess a treatment outside of its marketing authorization.

The committee notes that:

NHS England interprets the marketing authorisation that treatment ought to stop following progression to FAP stage 3;

Alnylam applied no formal stopping rule in their model so patients could continue treatment indefinitely;

[redacted] therefore believes that the committee is potentially introducing a significant uncertainty into their assessment of Alnylam model. The committee is attempting to use an economic model generating ICERs predicated on treatment in Stages 1 through 3 to estimate the costs and benefits of funding a treatment for Stages 1 and 2 only. [redacted] urges the committee to resolve this ambiguity as it is required for NICE to review treatments within their license i.e. with a stopping rule applied to patients in FAP stage 3.

Onpattro | European Medicines Agency. at Https://Www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Onpattro#authorisation-Details-Section. Date of Issue: August 2018. N.d.

The ECD makes two comments which are ambiguous regarding the clinical effect of patisiran. It would be helpful to have these sections reworded to remove the ambiguity.

Suppression of amyloid production

The committee indicates that evidence showed that patisiran offers considerable benefit for some patients. This immediately follows a sentence which describes how while TTR production is supressed, the body is able to clear accumulated amyloid deposits. This gives the impression that the committee believes that there is evidence that patisiran can clear amyloid deposits, a belief supported by an earlier observation that the clinical experts described that a reduction of amyloid deposits in all organs has been seen in the medical imaging of some patients.

To our best understanding of the evidence submitted by Alnylam, there is no direct peer-reviewed evidence of amyloid regression in patients on patisiran.

[redacted] request the committee clarify whether the judgement that patisiran offers benefit for some patient was influenced by a belief that it could clear or reduce amyloid deposits. If so, [redacted] further request that the evidence on which the committee formed this judgement is made available, if it can be made public. Alternatively, these sections could be reworded to avoid ambiguity.

The ECD makes two comments which are ambiguous regarding the clinical effect of patisiran. It would be helpful to have these sections reworded to remove the ambiguity.

ECHO as measurement of TTR

The committee describe how Other outcomes collected in the trial included assessment of serum transthyretin (TTR) levels and cardiac function (through echocardiogram and cardiac biomarkers such as troponin I and N-terminal pro-B-type natriuretic peptide [NT-proBNP]). It is unclear whether the examples of cardiac function assessment are also supposed to apply to assessment of serum transthyretin. This would not be unexpected (as there is some literature on the use of echocardiogram for the assessment of TTR levels) (Tsang and Lang 2010), although the sentence overall is ambiguous without an Oxford comma.

A reduction in echocardiogram measurements has not been established as a direct measure of amyloid removal as it is unclear what specifically is being measured, and therefore if the committee has understood echocardiogram to be a measure of both TTR levels and cardiac function more evidence would be required to conclude that the outcome of the echocardiogram is measuring TTR directly and not an unexpected confounder.

[redacted] request the committee clarify whether they understand TTR levels to have been measured directly by echocardiogram, and if so to further clarify what evidence they have used to justify a link between echocardiogram measurements and amyloid removal. Alternatively, this section could be reworded to avoid ambiguity.

Tsang, Wendy, and Roberto M. Lang

2010 Echocardiographic Evaluation of Cardiac Amyloid. Current Cardiology

Reports 12(3): 272“276.

Treatment discontinuation

The ECD does not specify which criteria were used to select the treatment discontinuation curve used. [redacted] wishes to draw the committees attention to whether the curve best reflecting the clinical context of hATTR disease was adopted to model treatment discontinuation, as this can significantly alter ICER and is a point of contention in many models involving discontinuation assumptions.

Patient choice

The ECD does not discuss patient and carer burden associated with patisirans mechanism of administration (once every 3 weeks by intravenous infusion), other than to note that infusion-related reactions are a relatively common adverse event. It is fairly concluded that continuous infusion is a relatively burdensome method of administration, and there is evidence that method of administration is important to patients; in a recent Amyloidosis Research Consortium UK patient survey (Amyloidosis Research Consortium UK, 2018 (Unpublished)), 50% of patients rated mode of administration as important or very important, and 59% rated place of administration as important or very important. In addition to the increased costs of infusion captured in the Alnylam economic model, there are also additional costs for patients and carers such as transport and the opportunity cost of paid employment foregone.

This is notable, as this represents the only genuine reason for differences between the BSC arms of the patisiran submission and submissions for other hATTR therapies. It would be helpful if NICE could clarify what the value of patient choice would be with respect to avoiding the cost and burden of continuous infusion methods of administration.

Amyloidosis Research Consortium UK. Burden of Disease and Perspectives on Treatment: Summary Report from Research with Hereditary Transthyretin Amyloidosis (HATTR) Patients and Carers. July 2018 (Unpublished). N.d.

Expectation of an increase over time in clinical benefit of patisiran

[redacted] notes that a greater level of TTR reduction was observed among patients receiving patisiran between months 9 and 18 of the APOLLO study than was observed between baseline and month 9 of the study. It remains unclear how Alnylam has justified their claim that this rate of change will persist in the long term. Indeed, as the mechanism of action of patisiran is to reduce serum TTR levels it is logical that after the initiation of treatment, patients who discontinue due to adverse events and lack of response to treatment will no longer be assessed for outcomes from patisiran treatment. Therefore, it is intuitive that there will be an increased mean reduction in TTR levels once these discontinuers are no longer observed. However, once use of treatment has stabilised there is no basis to assume that TTR levels continue to reduce at the observed rate. [redacted] suggests that further consideration be given to the expectation of persistent reduction in TTR among patients receiving patisiran.

With regards to the remaining evidence for long-term effect of patisiran, we note that these are anecdotal observations of single patients and it is not appropriate that they be reported under the clinical trial results heading. While patient experience is important, anecdotal reporting of a single patients experience may not be

representative of the mean effect of treatment.

Mean serum transthyretin (TTR) reduction at 18 months from the APOLLO study

[redacted] notes the committees judgement that it is important that patisiran generates a clinical benefit above a threshold of 80.0% that clinical experts advised was needed to halt or reverse neuropathic progression. There is general agreement among experts in the amyloidosis community that TTR reduction is closely associated with clinical benefits in ATTR amyloidosis. Given that the mechanism of action of inotersen is mediated through TTR, it is unsurprising that there will be an association between TTR levels and patient outcomes. However, there is no clear evidence to suggest that there is a threshold after which patients will have a clinically important improvement in prognosis. A TTR serum level reduction threshold may be established over time based on data from large sample sizes, but the heterogeneity of the patient population makes this challenging. There is no evidence that supports the use of a binary 80% threshold in TTR serum reduction as a criterion for long-term clinical benefits, as put forward by the committee, without providing a reference. Factors that are critical to the accurate measurement and interpretation of TTR include, for example:

The timepoint at which TTR is assessed after initiation of treatment; for example, at 3 versus 6 versus 9 months.

Whether the threshold criteria is established on first-line patients or all patients

Whether and how to take into account the pre-dose mean TTR

Whether and how to correct for specific mutations identified in hATTR

Whether and how to correct for important patient-specific factors, such as range of organ involvement, age at diagnosis, time from diagnosis to treatment and so on

The claimed threshold is inconsistent even with the patisiran submission own data; the correlation plot showing TTR reduction against clinical response (Figure 1 in this document, Figure 3 in Adams et al, 2018) includes a number of patients who do not improve with a >80% reduction and some who do improve with a <80% reduction. In addition, the plot contains both placebo and active treatment arms, meaning that confounding could occur if both TTR reduction and outcomes are correlated with taking treatment (which we would expect them to be). If the committee are certain that a threshold is clinically justifiable, we would request that the correlation is presented using the active treatment arm only and with a more rigorous methodology.

However even if a threshold is appropriate, the measurement of serum TTR levels in the submission is unclear and so it cannot be concluded that patisiran generates clinical benefit above this threshold. There is a general lack of scientific rigor, statistical methodology and consistency in the way that TTR reduction is measured and reported for patisiran. This has led to a number of apparent inconsistencies, which are described in comment 10 'inconsistencies in TTR reduction in submission' owing to space limitations

'Inconsistencies in TTR reduction in submission'

1. The 87.8% TTR reduction at 18 months is described in section 4.8 as being the mean reduction. This is not correct; the figure is actually the mean max reduction

according to Alnylam other publications (Adams et al. 2018). This is not a measurement with a well-understood statistical interpretation, but we believe the mean max might refer to the highest individual datapoint per patient out of many possible datapoints, without consistency in timeframe of measurement. However, we are unaware of a statistical definition of mean max, cannot find any support for this statistical approach in references, and have been advised by statistical experts that it is not a valid way to report data and therefore are unsure if this interpretation is correct. Regardless, to describe it simply as the mean reduction would ignore this methodological debate.

2. Alnylam reports a mean TTR reduction of 83% and 84% at month 9 and month 18, without reporting data at the many other timepoints for which they measured TTR reduction. However, in the appendix to the NEJM article (Adams et al. 2018) it states that the TTR reduction measurements were taken post dose. It is typical to take biomarker measurements pre-dose as is done consistently in other clinical trials. Taking a sample post-dose may lead to a larger decrease due to immediate impacts of patisiran dosing, but it is not a valid methodology for determining reduction over time. We believe the pre-dose results of TTR reduction for patisiran at all timepoints should have been reported, and if this convention was purposefully not followed it should be highlighted and explained in the ECD why a different approach was used.

3. It is unclear what the most important timepoint is for measuring TTR reduction to predict clinical outcomes. In AL amyloidosis, survival is predicted based on Light chain precursor protein reduction at 3 months and 6 months, but no data has established a later timepoint for that disease. Taking into account the lack of information to know when the most appropriate timepoint of measurements to predict the best response, we believe the most appropriate measurements to report would be the pre-dose mean (not mean max) and median of the whole sample at month 3, 6, 9, 12, 15 and 18.

[redacted] requests the committee reconsiders the appropriateness of an 80% TTR threshold, and the appropriateness of Alnylam reporting of their TTR outcomes which allow them to meet this threshold.

Patisiran for treating hereditary transthyretin-related amyloidosis: A Highly Specialised Technology Appraisal

ERG commentary on the company's response to the ECD and additional economic analyses

John W Stevens

Paul Tappenden

Aline Navega Biz

School of Health and Related Research (ScHARR)

22nd January 2019

1. Introduction

In December 2018, the National Institute for Health and Care Excellence (NICE) issued its Evaluation Consultation Document (ECD) on the use of patisiran for treating hereditary transthyretin-related amyloidosis (hATTR amyloidosis).[1] The ECD makes the following recommendation:

"1.1 Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults.
1.2 This recommendation is not intended to affect treatment with patisiran that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop." (NICE ECD,[1] page 3).

Following the publication of the ECD,[1] the company (Alnylam Pharmaceuticals) submitted a response[2] to this document which broadly focusses on four main issues:

(1) The appropriateness of a model structure in which health states are defined by polyneuropathy disability (PND)
(2) Evidence supporting the company's approach for modelling health-related quality of life (HRQoL)
(3) Additional analyses of the company's model including an alternative EQ-5D regression model and PND band-specific caregiver disutilities

[redacted]

This document presents a brief discussion and critique of the company's ECD response.

2. ERG commentary on the main points raised in the company's ECD response

2.1 Appropriateness of the model structure based on PND

The ERG's views regarding the company's model structure can be found in the ERG report[3] (Section 5.3.3, critical appraisal point (4), pages 111-114). The ERG has not changed its views regarding these issues but notes the following points regarding the company's choice of adopting a model structure based on PND and N-terminal pro b-type natriuretic peptide (NT-proBNP).

- The clinical advisors to the ERG believed that the company's model structure was reasonable. The clinical advisors noted that PND is limited in that it only reflects patients' mobility and does not capture symptoms relating to autonomic dysfunction.
- The NICE ECD[1] (Section 4.12) states that the Appraisal Committee believed that the company's model structure was broadly reasonable but noted that it did not capture all aspects of the condition. The ERG believes that the use of a model structure which is defined by PND

and NT-proBNP score, but which excludes states or events associated with other key impacts of the disease (i.e. autonomic dysfunction), is a limitation. This introduces uncertainty around the expected cost-effectiveness of patisiran.

- The ERG understands that the company's approach to modelling improvement (patisiran) or worsening (best supportive care [BSC]) in EQ-5D within each PND health state is an attempt to reflect those aspects of the disease which are not captured in the company's definition of the model health states (i.e. by PND). The ERG believes that the key issues relate to difficulties in defining which aspects of health are valued in a given PND state and whether the company's EQ-5D regression with upper and lower caps that can be achieved adequately reflects those factors. Given the company's view that a patient's health status can change within a given PND state, this suggests that PND alone is not a good descriptor of HRQoL. Issues relating to the evidence used to inform the HRQoL parameters are discussed in Section 2.2.
- The ERG notes that defining the model structure according to familial amyloidotic polyneuropathy (FAP) stage would have required fewer health states relative to a model defined according to PND. This would have required the available data from APOLLO to be "stretched" less but may have resulted in a more "blunt" model which is less sensitive to changes in the patients' underlying health states. The ERG agrees with the company that this would not have fully addressed issues relating to the definition of the model health states.
- The company's ECD response[2] (page 5) suggests that the company's base case analysis is conservative in that if autonomic dysfunction had been included in the model, the incremental cost-effectiveness ratio (ICER) for patisiran would be lower. The ERG believes that the company's model is likely to be implicitly capturing some impacts of autonomic functioning e.g. through PND-related mortality; given the evidence used to populate the model, the ERG is uncertain regarding the extent to which these effects are included.
- The tafamidis model submitted to AGNSS,[4] the Akcea model submitted to inform the NICE Highly Specialised Technology (HST) appraisal of inotersen,[5] and the inotersen and patisiran models reported by the Institute for Clinical and Economic Review (ICER)[6] each used FAP as the basis for describing the model health states.
- Page 6 of the ECD response[2] presents the company's justification for adjusting the observed patient count data from APOLLO to reflect a 6-month cycle duration. The company encountered problems in applying this adjustment; these issues are partly a consequence of sparsely populated transition matrices (for patisiran, 29 of 144 cells have events; for BSC, 19 of 144 cells have events). The matrices would not have required any adjustment if a longer cycle duration had been selected. In addition, using the 9-month time-point would have resulted in additional information being included in the model and may have produced a different extrapolation across the PND states. Whilst the ERG has concerns regarding the company's

transition matrices, these have less influence on the ICER than the company's HRQoL assumptions (see Section 2.2).

2.2 Evidence supporting the company's approach for modelling HRQoL

The ERG's views regarding the company's modelling of HRQoL conditional on PND score and time can be found in the ERG report[3] (Section 5.3.3, critical appraisal point (7), pages 119-122). Overall, the ERG considers the company's approach to modelling HRQoL to be unreliable. The ERG has not changed its view regarding these issues, but notes the following:

- The company's approach to modelling HRQoL over time is a key driver of the ICER for patisiran versus BSC. Exploratory analyses in which HRQoL is assumed to remain constant within each PND state increased the ERG's preferred ICER from [redacted] per quality-adjusted life year (QALY) gained to in excess of [redacted] per QALY gained (ERG report,[3] Table 34).
- As noted on page 7 of the company's ECD response,[2] the company provided an expanded regression model during the clarification stage of the appraisal[7] (clarification question B15). This model was not included in the ERG's preferred analyses as it still relied on the assumption of a constant rate of improvement/worsening and still applies minimum/maximum constraints; as shown in Section 2.3, the inclusion of this expanded regression model reduces the ICER for patisiran versus BSC by around [redacted]. The company's predicted utility profiles for patients in a given PND state receiving patisiran or BSC based on the expanded EQ-5D regression model are shown in [redacted] and [redacted], respectively.
- The maximum/minimum utility caps are particularly important as for most health states, these override the predictions of the regression equations after 5-6 years. The sources of these maximum/minimum caps are summarised in
- Table ***1***; these are based on the 25th/75th percentiles of the EQ-5D scores for each PND state across either treatment group at any assessment time point (baseline, 9 or 18 months). The ERG believes that the selection of these values is arbitrary.
- The interpretation of what these model parameters are intended to represent is not immediately obvious. For example, the ERG believes that the maximum caps are intended to represent the mean best achievable EQ-5D score for a patient in a given PND state with an undefined level of improvement in other hATTR amyloidosis-related symptoms (possibly, but not specifically, relating to autonomic dysfunction and/or cardiac-related symptoms). It is unclear if the values of the company's caps reflect these health states.
- In the absence of a clear definition of these aspects of a patient's health status, it would be difficult to elicit these values from clinical experts.

- The company argues that the HRQoL of a patient in a given model health state can change over time. The ERG agrees with this view. For example, a model defined by two health states "alive" and "dead" would be adequate for assessing changes in HRQoL as patients age, but would be inadequate for assessing the benefits of a treatment for a particular disease because the disease and its treatment are not captured in the definition of the health states.
- Page 7 of the company's ECD response[2] states that the clinical experts at the National Amyloidosis Centre (NAC) supported the company's HRQoL approach. However, it is unclear whether the experts were asked to interpret the definition of the maximum/minimum utility caps and their values, or whether these met with their expectations regarding additional mean health gains/losses over and above PND.
- The model of tafamidis submitted to AGNSS,[4] the Akcea model used in the NICE HST of inotersen,[5] and the models of inotersen and patisiran reported by ICER[6] do not assume continuously improving/worsening HRQoL in each FAP state. The ERG considers it reasonable to explore the impact of using alternative HRQoL estimates from the literature on the ICER for patisiran; the ERG agrees with the company that the use of Brazilian EQ-5D estimates from the Stewart study within an English population is subject to limitations.
- The company draws a comparison between approaches used to characterise HRQoL in the patisiran model in hATTR amyloidosis and the ocrelizumab model for relapsing/remitting multiple sclerosis (RRMS). However, these approaches are not comparable - the ERG does not believe that the ocrelizumab model included an assumption that mean HRQoL in a given Expanded Disability Status Scale (EDSS) health state can improve over time as a consequence of treatment effects on other disease-related factors beyond the EDSS.
- The company analysed EQ-5D utility scores using a repeated measures mixed-model; the data were the change from baseline at 9 and 18 months. The model allows estimation of the response at 9 and 18 months, whereas the company interprets the results as though time was fitted as a continuous variable and claims that *"neither of these curves was approaching a plateau by trial end."* The ERG believes that this is an over-interpretation of the model results.
- The ERG believes that company's use of maximum/minimum utility caps is a consequence of inappropriately extrapolating results from the repeated measures mixed-model. The ERG suggests that the company should consider alternative models that better represent the data.

[redacted]

[redacted]

[redacted]

[redacted]

Table 1: Value and source of minimum/maximum caps for health utilities in the company's original and revised models

PND score	Minimum cap	Minimum cap (applied only to BSC group)	Maximum cap	Maximum cap (applied only to patisiran group)
PND 0	[redacted]	Patisiran group 25th percentile at 9 months	[redacted]	Patisiran group 75th percentile at 9 months
PND I	[redacted]	Placebo group 25th percentile at 18 months	[redacted]	Patisiran group 75th percentile at 18 months
PND II	[redacted]	Placebo group 25th percentile at 18 months	[redacted]	Patisiran group 75th percentile at 18 months
PND IIIA	[redacted]	Placebo group 25th percentile at 9 months	[redacted]	Patisiran group 75th percentile at 9 months
PND IIIB	[redacted]	Patisiran group 25th percentile at 9 months	[redacted]	Patisiran group 75th percentile at 18 months
PND IV	[redacted]	Placebo group 25th percentile at 9 months	[redacted]	Patisiran group 75th percentile at 18 months

2.3 Additional issues raised in the company's ECD response

The company's ECD response[2] includes comments on a number of other factors relating to the model and its interpretation by the Appraisal Committee. A number of these issues relate to matters for the Appraisal Committee to address, rather than the ERG. The ERG makes the following comments:

- Page 16 of the company's ECD response[2] states that *"we removed all mortality due to polyneuropathy (i.e., not using the data from Suhr et al. [1994]) … implementing this change yields a significant reduction in the ICER compared with the result of the base-case model in the CS."* The cause of death in Suhr *et al* is not clearly reported. Despite the limitations of this study, mortality risk is reported to be higher in those patients with higher PND scores.
- The ERG believes that the company's inclusion of PND-related caregiver burden may be reasonable.
- The ERG's views regarding the company's elicitation of resource use impacts are presented on pages 123-124 of the ERG report.[3] The ERG has no additional comments.
- The ERG's views regarding discount rates are presented on pages 107-108 of the ERG report.[3] The ERG has no additional comments.

2.4. Additional analyses of the company's model including an alternative EQ-5D regression model, PND band-specific caregiver disutilities, with/without commercial access scheme proposals

Table 3 presents the results of the company's new analyses for the ERG's original preferred analysis,[3] and two additional scenarios presented within the company's response - "Scenario A" and "Scenario B."

Scenario A includes two additional amendments:

(i) The use of the expanded regression model provided during the clarification stage of the appraisal.[7] This model includes the following covariates: treatment group; time; PND score; NT-ProBNP, and a treatment-by-time interaction term.

(ii) The inclusion of PND-specific disutilities for caregivers (assuming one caregiver) based on estimates applied in the NICE HST inotersen model,[5] which were in turn taken from a previous economic analysis of natalizumab for RRMS.[8]

Scenario B is the same as Scenario A, except that PND-related mortality has been removed from the model; this is equivalent to ERG exploratory analysis number 11 (see ERG report,[3] Table 34).

Table 2: Results of ERG-preferred analysis and company's Scenarios A and B (excluding commercial access agreements)

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG-preferred analysis*							
Patisiran	15.81	7.20	[redacted]	7.42	6.86	[redacted]	[redacted]
BSC	8.38	0.33	[redacted]	-	-	-	-
Company's Scenario A							
Patisiran	15.81	6.96	[redacted]	7.42	7.14	[redacted]	[redacted]
BSC	8.38	-0.18	[redacted]	-	-	-	-
Company's Scenario B							
Patisiran	18.15	7.70	[redacted]	3.62	9.67	[redacted]	[redacted]
BSC	14.53	-1.97	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group

**The base case includes the initial distribution provided by the company, instead of the distribution used in ERG preferred model in the report. This results in a minor difference between the ICERs in the ERG report and the company's ECD response*

The ERG's preferred scenario suggested that the deterministic ICER for patisiran versus BSC was [redacted] per QALY gained. The incorporation of the company's expanded regression model and PND-specific carer disutilities (Scenario A) leads to a lower deterministic ICER of [redacted] per QALY gained. The removal of PND-related mortality (Scenario B) reduces the ICER further to [redacted] per QALY gained. The ERG was able replicate the company's results for these scenarios and believes that

these analyses have been implemented without error. As noted in the original ERG report,[3] removing PND-related mortality from the model (Scenario B) improves the ICER for patisiran; this is partly because under this scenario, patients in the BSC group survive longer across a distribution of PND states which are valued, on average, worse than death. This highlights the importance of the company's minimum/maximum utility caps (see Section 2.2).

2.5 [redacted]

Table 3: [redacted]

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
[redacted]							

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Analysis B1:	[redacted]						
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Analysis B2:	[redacted]						
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Analysis B3:	[redacted]						
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Analysis B4:	[redacted]						
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group

3. References

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4. Faria R, Walker S, Palmer S, Corbett M, Stirk L, McDaid C. Tafamidis for Transthyretin Familial Polyneuropathy (TTR-FAP) Evidence Review Group assessment of manufacturer submission: CRD; 2012.
5. Akcea Therapeutics. Inotersen for treating hereditary transthyretin amyloidosis [ID1242] - Company's submission to NICE Boston, MA; **2018**.
6. Institute for Clinical and Economic Review. Inotersen and patisiran for hereditary transthyretin amyloidosis: Effectiveness and value - Evidence Report; 2018.
7. Alnylam Pharmaceuticals. Patisiran for treating hereditary transthyretin-related amyloidosis [ID1279] - company's response to clarification questions from the ERG. Cambridge, Massachusetts; 2018.
8. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics* 2008;26:617-27.

Recieved via email: 28 February 2019

Dear Anant

We have now had an opportunity to review the consultation response to the ECD along with the ERG response.

On reflection, there are a few outstanding items that it would be useful to resolve before we take this topic back to committee. We would like to highlight them as quickly as possible to give you an opportunity to see if they can be addressed before the February committee meeting.

1. Please provide and alternative utility regression model which does not rely on maximum and minimum utility caps: we ask you to fit a more sensible model to the data which a) accounts for the characteristics of EQ-5D data (e.g. a Tobit model) so that it is no longer necessary to restrain the estimates by applying arbitrary maximum and minimum values and b) which includes main effects as well as interaction terms.

   ALNYLAM RESPONSE: We believe that the definition of a more sophisticated model like the Tobit, which is designed to estimate linear relationships between variables when there is either left- or right-censoring in the dependent variable, would not solve the principal issue raised by the ERG, which is related to the implementation of maximum and minimum utility caps.

   In implementing a tobit model, one is defining ex-ante the maximum and minimum utility caps as an intrinsic characteristic (the censoring) of the dependent variables. In the regression analysis we have submitted for consideration, we considered a linear model and applied the maximum and minimum utility caps ex-post. In either case, a choice is made to restrain the maximum and/or minimum values generated by the model.

   As described in our ECD response, the difference in utility (HRQoL) between the patisiran and placebo treatment arms continue to diverge over time without attenuation at the end of the 18-month APOLLO study. The APOLLO study is the world's largest, longitudinal dataset of hATTR amyloidosis patients and is therefore the most appropriate dataset for deriving utilities for patients affected by this condition. However, there are still limitations to this dataset because utility values were collected at only two time points (9 and 18 months).

   The availability of only two data points limits the impact of any given model specification on the extrapolation of utilities – whether it is a linear model, a tobit model, or otherwise - since modelling data from two data points leads to fundamental limitations in the model.

   Given these fundamental modeling constraints, we assigned maximum and minimum caps on utilities based on two evidence-based factors:

   - Capping data based on the central 50% of the distribution excludes outliers (i.e. 25th & 75th percentiles), while preserving the majority of observations in the APOLLO study
   - Capping of these utilities was supported by clinical opinion from the National Amyloidosis Center

2. Please clarify if the regression model is based on patient current PND state or PND state at baseline?

   ALNYLAM RESPONSE: The regression model is specified on the patients' PND Score base at the same time of measurement of the EQ-5D score. In other words, it represents the patients' current PND state.

3. Extrapolation of utility post 18 months: your model allows estimation of the response at 9 and 18 months, whereas you interpret the results as though time was fitted as a continuous variable and claim that "neither of these curves was approaching a plateau by trial end." The ERG believes that this is an over-interpretation of the model results. Please provide a sensitivity analysis of when treatment effect stops (similar to sensitivity analysis for hazard ratio)

   ALNYLAM RESPONSE: We do not agree with the premise of the request and it appears to be based on a misunderstanding of the model and related analyses, namely:

   1. The regression model does indeed consider time as a continuous variable;
   2. Since time is modeled as a continuous variable, the model allows for the estimation of the utility at any given time and not only at 9 and 18 months;
   3. The curves in Figure 2 of our submitted ECD response (about which we believe the ERG's question is based) are not presenting values generated by the regression model but actual observed data from the APOLLO trial;
   4. Consequently the sentence that "neither of these curves was approaching a plateau by trial end" was not an interpretation of model result, but the observed clinical data from the study.

   Finally, the cited "sensitivity analysis for hazard ratio" with a similar treatment effect stop doesn't seem to exist in our submission nor it has previously been undertaken by the ERG, so we are not clear what the ERG is seeking here.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Please can you confirm if you are able to explore and address these issues. Please note, In order to ensure we are able to continue with the February meeting, the information will be required to reach us by **noon, 31 January 2019**. Please let us know by close of play today if you are able to make this timeline. We are happy to have a call if you need any further clarity or answer any questions.

1. **Table 3:**

[redacted]

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4. *LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group*

Regards

Sheela Upadhyaya

Associate Director Highly Specialised Technologies

Patisiran ID 1279

Alnylam response to additional ERG/NICE questions regarding Alnylam's ECD response: Received 31 January 2019

"Dear Anant

Many thanks for joining the teleconference this afternoon with the NICE team and the ERG. I am following up by email to clarify what was discussed and the additional clarification we would like to see before the next committee meeting.

During the teleconference the ERG considered your response to our previous queries that providing an alternative regression model (Tobit) would not address the principal concern which was related to the use of caps to prevent implausible utility values. We are in agreement that it is not feasible to provide an alternative model at short notice but would like to you to provide the following information:

1. The way in which utility is extrapolated after 18 months applies a constant improvement in the patisiran arm and constant decline in the BSC arm. Please provide sensitivity analysis which explores alternative assumptions whereby the duration of treatment benefit is limited by time."

ALNYLAM RESPONSE: Based on the discussions with NICE and the ERG on 31 January 2019, we have produced the sensitivity analyses based on the following changes:

We completely removed the maximum/minimum constraints applied to utilities in the model, which were originally based on the central 50% (i.e. using 25th and 75th perecentiles) of the distribution of observed data from the APOLLO trial. (Please see our original response to prior ERG questions, our ECD response, and our most recent reply to your emailed questions).

We then incorporated an attenuation of benefit for patisiran based on the arbitrary periods of time as requested by the ERG (note that was applied these to BOTH the patisiran and the BSC arms) to:

a. 7 years
b. 5 years (Note: The ERG states in its response to our ECD comments that the constraints on minimum/maximum values override the regression equation outputs in 5-6 years)
c. 4 years

Please note that the application of the above arbitrary limits to the utility decline in the BSC arm are highly conservative as they assume the disease course in the untreated BSC patients suddenly stops worsening, which is clinically implausible. This is in direct conflict with expert clinical opinion we received from the National Amyloidosis Centre (June 13th meeting between Alnylam and NAC). If an approach were taken to follow the NAC opinion, the ICERs reported below would be lower. The limited time granted to us by NICE has not afforded us the opportunity to pursue alternative modelling in further detail.

The tables below report the results of these analyses on base case model A (ERG approach + all regression terms + revised carer disutilities) and on base case model B which address all

criticisms from the Committee (ERG approach + all regression terms + revised carer disutilities + removal of mortality associated with PND). Please see our ECD response for more information on the revised base case. Note that the results presented below include the approved simple PAS. We find that the results remain relatively stable, demonstrating what we discussed with NICE and the ERG on our last teleconference (namely, that the application of minimum/maximum utility caps is a conservative approach versus allowing the regression equation – which itself is based on the observed APOLLO trial data – to run through for the entire extrapolation period).

Table 1. Summary of the scenario analyses on time limits for the EQ-5D regression function.

ICERs/QALY gained	**Model A**	**Model B Addressing Committee Concerns**
Base case	[redacted]	[redacted]
Time limit at 7 years	[redacted]	[redacted]
Time limit at 5 years	[redacted]	[redacted]
Time limit at 4 years	[redacted]	[redacted]

[redacted]

2. "We note that clinical expert opinion was sought to validate the utility values in the model. Please provide further information in particular whether clinical advice was requested on the suitability of the utility caps or whether the experts were asked to validate the clinically plausibility of the modelled utility profile within the PND health states."

ALNYLAM RESPONSE: Please find below excerpts of the notes taken by the interviewer during meetings with the NAC to obtain clinical advice.

The validation of the Patisiran CEA Model consisted of a series of consultations with UK top clinical experts that took place September 28th, 2017; June 13th, 2018; and December 19th, 2018. The input received in these consultations are reflected in the following sections of our main Company Submission (CD): 12.1.2, 12.1.3, 12.1.5; 12.2.1; 12.2.2; and 12.2.5.

I. The September 28th, 2017 meeting took place at the National Amyloidosis Center (NAC) with Prof. Philip Hawkins and Prof. Julian Gilmore from the NAC, and Prof. Mary Reilly from the National Hospital for Neurology and Neurosurgery. The objectives of the meeting were to present the concept design of the cost-effectiveness model that was being developed and to test the clinical plausibility of its design and assumptions.
    a. In the meeting we presented the following:
        i. The general model structure with health states based on the PND Scores

1. The clinicians thought it was a reasonable approach. They also explained that PND Score is a well understood scale and used in routine clinical practice

ii. The model cardiac health states based on NT-proBNP

1. The clinicians thought it was reasonable approach and one that was important to reflect the reality of UK patients
2. The clinicians also recommended to use the soon to be published Gillmore paper (Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis [published online ahead of print, 20 October 2017]. *European heart journal.* 2017) to get mortality risk.

iii. Advice on how to project patisiran and BSC clinical effects beyond 18 months:

1. The three clinicians recommended that we should assume that patisiran benefit will continue to improve beyond 18 months while BSC patients will continue to worsen as per the natural history of the disease.

II. The June 13th, 2018 meeting took place at the NAC with Prof. Philip Hawkins and Prof. Julian Gilmore. The objective of the meeting was to get external validition of the patisiran CEA model intended for the HST submission

a. With respect to validation of the utilities in the model, we addressed the following with both experts:

i. We presented the output in the model that showed that TQoL is different by treatment and it changes over time within the same health state (PND Score)

1. They felt that it is reasonable and would indeed expect to observe different utilities for patients in patisiran and best supportive care within the same PND score, as was observed in the APOLLO trial. They said that our health states, as defined by PND Score, are not just capturing the functional aspects of the diseases but also capturing the autonomic symptoms, which can progress at a different rate than the PND score. In fact, they stated their belief that QOL is driven mainly by the autonomic symptoms (diarrhea, constipation, wasting) and is thus a sufficient proxy for capturing autonomic aspects of the disease.

ii. We presented the extrapolations of the utility after the initial 18th months and asked then if the contraints imposed (i.e. capping by 25th and 75th perecentiles) was reasonable and if the resulting outputs were clinically reasonable

1. They agreed with the approach of capping to avoid implausible results, however, they felt it would be conservative to limit (cap) the decrease in TQoL for patients in best supportive care because once a patients start showing symptoms they would only get worse and never better, based on their clinical experience and the natural history of the disease.

III. The December 19th, 2018 meeting took place at the National Amyloidosis Center (NAC) with Prof. Philip Hawkins and Prof. Julian Gilmore from the NAC, and Prof. Mary Reilly

from the National Hospital for Neurology and Neurosurgery. The objective of the meeting was to address the Committee Concerns on the CEA model

a. In the meeting we presented to the three experts the following:
    i. We presented the committee concerns regarding the utilities varying by treatment and time within a PND Score. We presented them with the utility curves projected by the model. In addition, we presented EQ-5D data observed in APOLLO for those patients that did not change their baseline PND scores at the 18th month for both patisiran and placebo arms. We asked them their interpretation of the data and how it addresses the committee concerns.
        1. The three experts stated that the APOLLO data clearly support that TQoL will be influenced by treatment and time, so in their mind what the model is predicting is reasonable and clinically expected. They stated the following reasons to support their thinking:
            a. PND scores and FAP stages are broad classifications of polyneurapthy (PN) symptoms. PN symptoms may improve or worsen without the patient changing PND score or FAP stage
            b. Autonomic symptoms and polyneuropathy may improve or worsen within a PNS score or FAP stage.
            c. The natural history of the disease shows that untreated patients will continue to get worse as time progresses, so it is reasonable to expect their perceived TQoL will get worse with time even within a PND score
    ii. We presented the committee concerns regarding the model extrapolation of utilities beyond the initial 18 months. We presented the utility curves projected by the model. We discussed teir thoughts on the approach of capping the utilities and if the extrapolation made clinical sense
        1. They thought that capping the utilities is a reasonable approach to avoid implausible results.
        2. They also thought the curves made clinical sense because they will expect the amyloid deposition to reduce treatment with patisiran, which they expect to yield clinical benefits in the long term, while patients in best supportive care will only get worse with time.

3 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Patisiran for treating hereditary transthyretin-related amyloidosis: A Highly Specialised Technology Appraisal

ERG commentary and additional analyses around health utility constraints and access proposals

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6th February 2019

1. Introduction

This document provides a brief commentary on the company's sensitivity analyses and access proposals undertaken by the company (received 2nd February 2019).[1] The company's new sensitivity analyses impose time-dependent constraints on the maximum level of improvement in health utility for patients in the patisiran group and on the maximum level of worsening in health utility for patients in the BSC group. Separate analyses are presented for "Scenario A" and "Scenario B". As noted in the previous ERG addendum,[2] Scenario A includes two additional amendments to the ERG-preferred model:

(i) The use of the company's expanded regression model provided during the clarification stage of the appraisal.[3] This model includes the following covariates: treatment group; time; PND score; NT-ProBNP, and a treatment-by-time interaction term.

(ii) The inclusion of PND-specific disutilities for caregivers (assuming one caregiver) based on estimates applied in the NICE HST inotersen model,[4] which were in turn taken from a previous economic analysis of natalizumab for RRMS.[5]

Scenario B is the same as Scenario A, except that PND-related mortality has been removed from the model; this is equivalent to ERG exploratory analysis number 11 (see ERG report,[6] Table 34).

The company's addendum also applies a combination of three access proposals to each of Scenarios A and B including: (i) no time-dependent utility constraint and (ii) a 5-year utility constraint.

2. Critique of the company's new results

2.1 Verification of implementation of company's new analyses

Based on information provided by the company, the ERG has been able to replicate the analyses presented in the company's addendum.

The ERG is satisfied with the company's approach to implementing the time-dependent utility caps; however, these are limited to only three timepoints (4, 5 and 7 years). The ERG believes that it may be appropriate to consider a broader range of timepoints; this is explored in additional analyses by the ERG (see Sections 2.2 and 2.3). The maximum and minimum caps used in the ERG's analyses are summarised in Table 1.

The ERG is not satisfied with the company's implementation of the combined access schemes as these are subject to errors in logic; these issues are discussed in Section 2.3. Additional ERG analyses are presented which address these concerns.

Table 1: Maximum and minimum caps for health utilities (excluding general population utility constraints)

	Maximum cap (applied only to patisiran group)						**Minimum cap (applied only to BSC group)**					
PND score	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV	PND 0	PND I	PND II	PND IIIA	PND IIIB	PND IV
Original model (Scenario A)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.2 Critique of company's sensitivity analyses

Briefly, the company's new sensitivity analyses suggest the following:

- Across all utility scenarios, the ICER for Scenario B is more than [redacted] per QALY lower than the ICER for Scenario A. Scenario B does not reflect ERG's preferred scenario; whilst there is uncertainty surrounding the relationship between PND score and mortality risk, the ERG's clinical advisors believed that increased PND is likely to be associated with increased mortality risk. The ERG has not considered this scenario further in this addendum.
- Based on time-dependent maximum/minimum utility caps of 4 or 5 years for all model health states, the ICER for patisiran remains similar to the base case scenario, whereby utility caps were defined according to the 25th/75th percentiles of the EQ-5D scores from APOLLO. This is because the IQR-based caps take effect around these timepoints for most of the model health states (see ***[redacted] and ***[redacted]); as such, the impact on the ICER is minimal. When the utility caps are implemented at the 7-year timepoint, the ICER for patisiran is reduced by around [redacted]; this is because the patisiran group is assumed to accrue more QALYs, and the BSC group is assumed to generate fewer QALYs, relative to the company's base case.

[redacted]

[redacted]

[redacted]

For information, the ERG has undertaken an equivalent analysis using Scenario A over a broader range of utility cap timepoints (see Table 2). These analyses show that applying utility caps at timepoints of less than four years may lead to a marked increase in the ICER relative to the base case. The ERG notes that there is considerable uncertainty with respect to the duration of improvement/worsening in HRQoL associated with non-PND-specific symptoms in both treatment groups.

Table 2: Results of ERG-preferred analysis and company's Scenarios A and B (excluding commercial access proposals)

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's Scenario A							
Patisiran	15.81	6.96	[redacted]	7.42	7.14	[redacted]	[redacted]
BSC	8.38	-0.18	[redacted]	-	-	-	-
"Loss of effect" at 2 years							
Patisiran	15.81	6.06	[redacted]	7.42	5.59	[redacted]	[redacted]
BSC	8.38	0.47	[redacted]	-	-	-	-
"Loss of effect" at 3 years							
Patisiran	15.81	6.40	[redacted]	7.42	6.28	[redacted]	[redacted]
BSC	8.38	0.12	[redacted]	-	-	-	-
"Loss of effect" at 4 years							
Patisiran	15.81	6.66	[redacted]	7.42	6.83	[redacted]	[redacted]
BSC	8.38	-0.17	[redacted]	-	-	-	-
"Loss of effect" at 5 years							
Patisiran	15.81	6.88	[redacted]	7.42	7.28	[redacted]	[redacted]
BSC	8.38	-0.41	[redacted]	-	-	-	-
"Loss of effect" at 6 years							
Patisiran	15.81	7.07	[redacted]	7.42	7.66	[redacted]	[redacted]
BSC	8.38	-0.59	[redacted]	-	-	-	-
"Loss of effect" at 7 years							
Patisiran	15.81	7.21	[redacted]	7.42	7.95	[redacted]	[redacted]
BSC	8.38	-0.74	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group

2.3

[redacted]

[redacted]

Table 3: Results of company's Scenarios A [redacted]

	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG combination of commercial access agreement (Scenario A)							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 2 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 3 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 4 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 5 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 6 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
"Loss of effect" at 7 years							
Patisiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group

References

1. Pharmaceuticals A. Alnylam response to additional ERG/NICE questions regarding Alnylam's ECD response: (2nd February 2019); 2019.
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